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Consensus Development Conference
on the Management of
Clinically Localized Prostate Cancer

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Introduction

John E. Antoine¹

Prostate cancer, the second most common form of malignant disease in American men, is one of the most frequently diagnosed cancers in men over the age of 50, with the incidence increasing each decade after the age of 50. Approximately 96,000 new cases of prostate cancer will be diagnosed in 1988. According to the American College of Surgeons, more than one-half of these are clinically localized. Moreover, approximately 26,000 deaths each year are due to prostate cancer, the etiology of which is unknown. It is a common finding at autopsy in men older than 50 years. The most frequently observed histologic tumor type is adenocarcinoma.

Localized prostate cancer is usually discovered during the rectal part of a physical examination or detected incidentally in the histologic material from a transurethral prostatectomy performed for enlargement of the prostate. A needle biopsy is often diagnostic. Patients with localized disease may be asymptomatic at the time of the diagnosis of prostate cancer or may have symptoms of urinary retention; hematuria is uncommon.

The extent of tumor involvement (stage) is usually described by a classification system that has undergone evolution and modification over the years. Physicians have encountered difficulties in describing the extent of disease because of the use of more than one staging system and of staging based on clinical rather than surgical findings. Because of this lack of consistency in the staging systems, the analysis of data remains complex and difficult. Two accepted clinical staging systems are in use at this time. The American Urological System consists of A, B, C, and D stages, and the American Joint Committee uses the T, N, and M system. For proper comparison of alternative treatments for the management of localized prostate cancer, a uniform, tumor-extent, staging system is necessary. The degree of histologic anaplasia (malignancy) of the cells also appears to correlate with the patient's prognosis. The Gleason histologic scoring system is commonly but not uniformly used; the higher the Gleason score, the worse the prognosis. Standardization of a histologic grading system would also facilitate scientifically valid comparison of treatment modalities.

Radical prostatectomy has a long history as the definitive management for localized prostate cancer. The retropubic approach, which readily permits staging lymphadenectomy, has become more common than the perineal approach. Recently, the surgical technique has been refined to preserve the nerves essential for sexual potency.

Radiation therapy is another form of definitive treatment and is usually given by means of high-energy, external-beam photons from linear accelerators. An alternative form of radiation treatment is the implanting of radioisotopes in the cancer tissue.

Hormone therapy is an effective means of palliation for advanced prostate cancers. It is under renewed investigation as an adjuvant to definitive therapy of the primary tumor in early disease. Although chemotherapy generally has been used in the palliation of patients with advanced hormone refractory disease, its role in the management of localized prostate cancer remains to be defined.

Following treatment of prostate cancer, the follow-up of the patient includes physical examination, laboratory studies, and imaging examinations. Laboratory studies might include alkaline phosphatase and prostate-specific antigen. Imaging studies commonly include x-rays, bone scans, magnetic resonance imaging, computed axial tomography, and ultrasound. The optimal combination of laboratory and imaging studies has not been determined, but this area is evolving at this time.

Competing (noncancer) causes of death are common in the age group affected by prostate cancer. The natural history of this disease is variable, and some untreated patients may die without symptoms of prostate cancer. These factors make the significance of therapeutic intervention more difficult for the physician to assess for prostate than for other cancers.

The quality of life and sexual functioning can be affected by treatment for prostate cancer because impotence and incontinence can occur following treatment. Prospective studies that would determine how often these side effects are associated with each treatment have not been done. These aspects should be considered when the physician helps the patient choose the best course of treatment.

To evaluate new information and resolve issues regarding optimal treatment, the National Cancer Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference on the Management of Clinically Localized Prostate Cancer on June 15-17, 1987. The scientific material from the manuscripts published in this edition was presented at that consensus conference.

¹ Radiation Research Program, Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892.

Consensus Statement: The Management of Clinically Localized Prostate Cancer¹

National Institutes of Health Consensus Development Panel

Prostate cancer is the second most common form of malignant disease in American men. It is one of the most common cancers in men over the age of 50, with the incidence increasing each decade after the age of 50. Approximately 96,000 new cases of prostate cancer were expected to have been diagnosed in 1987, of which 50,000 may have been clinically localized, according to the American College of Surgeons. There are approximately 26,000 deaths from prostate cancer annually; it is a common finding at autopsy in men over the age of 50 years. The most common histologic tumor type is adenocarcinoma. The etiology remains unknown at present.

Localized prostate cancer is usually discovered by rectal examination performed during a physical examination or detected incidentally in the histologic material obtained from a transurethral prostatectomy being performed for enlargement of the prostate. Patients with localized disease may be asymptomatic at the time of the diagnosis of prostate cancer or may have symptoms of urinary retention.

The extent of tumor involvement (stage) customarily is described by a classification system that has undergone evolution and modification over the years. Difficulties in describing disease extent have arisen from the use of different staging systems and from staging based on clinical as opposed to surgical findings. Because of this lack of uniformity in the staging systems, the analysis of data remains complex and difficult. Two accepted clinical staging systems are in use. The system used by members of the American Urologic Association consists of A, B, C, and D stages, and the American Joint Committee on Cancer uses the T, N, and M system.

Radical prostatectomy has a long history as the definitive management for localized prostate cancer. The retropubic approach, which readily permits staging lymphadenectomy, has become more common than the perineal approach. Recently, the surgical technique has been refined to preserve the nerves essential for potency. Radiation therapy is another form of definitive treatment and is usually given by means of high-energy, external-beam photons (x-rays) with linear accelerators. Hormone therapy is an effective means of palliation; its role in the management of early disease is under renewed investigation as an adjuvant to definitive therapy of the primary tumor. Chemotherapy generally

has been used in the palliation of patients with advanced hormone-refractory disease.

After the completion of treatment of prostate cancer, the follow-up of the patient includes physical examination, laboratory studies, and imaging examinations. The exact combination of laboratory studies and imaging examinations has not been agreed upon, and this situation is undergoing evolution in the United States. The natural history of this disease is variable, and some untreated patients may die without symptoms of prostate cancer. Competing (non-cancer) causes of death are common in the age group affected by prostate cancer. These factors make the significance of therapeutic intervention more difficult to assess than in other cancers.

The general quality of life and sexual functioning (impotence) can be affected by treatment for prostate cancer. These aspects should be considered when the physician helps the patient to choose the best course of treatment.

To evaluate new information and resolve issues regarding optimal treatment, the National Cancer Institute and the Office of Medical Applications of Research of the National Institutes of Health convened a Consensus Development Conference on the Management of Clinically Localized Prostate Cancer on June 15-17, 1987. After 1½ days of presentations by experts and discussion by the audience, a consensus panel drawn from specialists and generalists from the medical profession and related scientific disciplines, clinical investigators, and public representatives considered the evidence. The panel agreed on answers to the following key questions:

- 1) What is the utility of pathologic assessment and imaging techniques in the staging of prostate cancer? When is pelvic node dissection necessary?
- 2) Who is the optimal candidate for radical prostatectomy? What is the morbidity of the procedure, and how can it be minimized with preservation of curative potential?
- 3) Who are the candidates for definitive radiation therapy? What methods are optimal, and what are the long-term results in terms of local control and survival? What is the morbidity of the procedures, and how can it be minimized with preservation of curative potential?
- 4) Should definitive radiation therapy, hormone therapy, and/or chemotherapy be used as adjuvant treatment in high-risk patients?
- 5) What directions for future research are indicated?

¹ Adapted from The Management of Clinically Localized Prostate Cancer, National Institutes of Health Consensus Development Conference Statement, vol 6, No. 10, 1987.

QUESTIONS AND ANSWERS

What is the utility of pathologic assessment and imaging techniques in the staging of prostate cancer? When is pelvic node dissection necessary?

An accurate histologic or cytologic diagnosis of cancer of the prostate is essential prior to the planning of treatment. The histologic diagnosis usually is established from a specimen obtained by core biopsy or transurethral resection. It may be obtained cytologically from a fine-needle aspiration. Histologic and/or cytologic grading and staging (extent of disease) are necessary in plans for appropriate treatment and provision of a prognosis.

There are several systems for grading prostate cancer that yield similar information, and all are based on the degree of tumor differentiation and growth patterns. The Gleason histologic grading system is based on five tumor patterns. The values of the predominant and the lesser patterns are added together to generate a numerical histologic score. Histologic grading correlates well with the biologic degree of malignancy, i.e., tumor invasion, metastatic spread, and mortality rate.

The nature of the specimen obtained by fine-needle aspiration usually precludes histologic but not cytologic grading based on nuclear anaplasia. Experienced observers find that cytologic grading yields results and information similar to those of histologic grading, but this requires further prospective correlation. The simplicity of fine-needle aspiration should increase its use. All tissue sampling techniques have a recognized risk of error.

Flow cytometry can be used to measure DNA content. Abnormal DNA content appears to be predictive of more aggressive biologic behavior. Additional study is required for the determination of its prognostic utility in routine practice.

Pelvic lymphadenectomy is a surgical staging procedure used when clinical decisions depend on accurate knowledge of the presence or absence of metastatic tumor in the pelvic lymph nodes. It is performed most commonly prior to a planned radical prostatectomy. Pelvic lymph node dissection continues to provide staging information that can be obtained by no other method.

Biochemical evaluation is critical to the initial staging assessment. Serum alkaline phosphatase and acid phosphatase determinations are helpful in identifying patients with metastatic disease. The serum prostate-specific antigen is elevated more frequently in men with prostate cancer than is the acid phosphatase and can be used to monitor response to both local and systemic therapies. Prostate-specific antigen is specific for prostate tissue but not for prostate cancer, which precludes its use in screening.

Anatomic imaging contributes to the staging assessment of patients presenting with prostate carcinoma. The initial evaluation requires isotopic bone scan, chest roentgenogram, and an imaging evaluation of the upper urinary tract. Although lymphography has been used in the past, its current applications are limited. More locally directed imaging techniques for clinical staging include transrectal ultrasound, computed tomography, and magnetic resonance imaging. It is essential that results of all

imaging examinations be carefully correlated with results of digital rectal examination, cystoscopy, and pertinent laboratory tests in the determination of the clinical stage of the cancer. Imaging equipment should be state of the art. There is no single best procedure, and all procedures have significant limitations in their accuracy.

The value of transrectal ultrasound is operator dependent; a dual-modality intrarectal probe should be used. Intraprostatic anatomy, capsular integrity, and the seminal vesicles can be imaged. Pelvic adenopathy cannot be demonstrated.

Computed tomography can help one assess the periprostatic area and lymph node size. Intraprostatic detail is poor, and masses rarely are identified. The detection of enlarged lymph nodes is highly sensitive, but normal-sized nodes may contain microscopic tumor.

Magnetic resonance imaging, like transrectal ultrasound, can demonstrate intraprostatic anatomy. The technique appears to be as accurate as computed tomography and transrectal ultrasound in the detection of periprostatic extension and seminal vesicle involvement. It is competitive with computed tomography in demonstrating pelvic adenopathy.

At present, scientific controlled studies are lacking in adequate patient numbers to permit other than a gross comparison of imaging methods. Clinical comparisons are biased by patient selection and nonblinded observer factors.

Who is the optimal candidate for radical prostatectomy? What is the morbidity of the procedure, and how can it be minimized with preservation of curative potential?

A radical prostatectomy includes the removal of the entire prostate and seminal vesicles with adequate resection margins by either a retropubic or perineal approach. The adequacy of surgical margins should be confirmed by a thorough pathologic evaluation. An appropriate candidate for definitive primary radical prostatectomy has a tumor that is localized to the prostate (stage A2, B1, or B2). The patient should be an acceptable surgical candidate and have no significant "comorbid" disease. Patients should have completed a negative staging evaluation for distant metastases. Ideally, pelvic lymphadenectomy should be performed with a retropubic prostatectomy and for high-risk patients having a perineal prostatectomy. Adequate staging information will be obtained with a "limited node dissection" that includes nodes within the boundaries of the external and internal iliac vessels and obturator fossa. This will minimize complications of lymphedema and lymphocele.

Radical prostatectomy is associated with both perioperative morbidity and late side effects. These complications can include urinary incontinence, urethral stricture, impotence, and morbidity associated with anesthesia and a major surgical procedure. Significant incontinence and stricture are uncommon. The incidence of impotence can be reduced with newer surgical techniques with an anatomical dissection that preserves nerves necessary for erection. The preservation of potency with this technique is achieved in a majority of patients, although it is related to tumor size and patient age. Attempts to preserve potency must not compromise adequate removal of the tumor.

Clinically evident local recurrence following radical

prostatectomy is not common. Cancer-free survival rates at 15 years for patients with cancer limited to one lobe of the prostate approach the expected survival of men in the general population in a comparable age group. Disease-free survival rates are less with larger tumors.

Who are the candidates for definitive radiation therapy? What methods are optimal, and what are the long-term results in local control and survival? What is the morbidity of the procedures, and how can it be minimized with preservation of curative potential?

Candidates for definitive radiation therapy must have a confirmed pathologic diagnosis of cancer that is clinically confined to the prostate and/or surrounding tissues (stage A2, B, or C). Patients should have completed a negative staging evaluation for distant metastases.

An effective radiation therapy regimen should deliver a homogeneous dose to the entire tumor volume. Such a dose is delivered most commonly by external-beam radiation therapy. In selected instances, interstitial irradiation can be delivered with or without external-beam radiation therapy when the disease is confined to the prostate. Although lower local control rates have been reported with interstitial therapy, efforts are being made to improve these results by careful attention to technique and dosimetry. Newer radiation modalities such as particle therapy are under active investigation. Local tumor in the prostatic and periprostatic tissue can be controlled effectively by irradiation. However, the impact on overall survival of treating the regional lymph nodes is unclear.

Definitive radiation therapy is associated with both acute and chronic effects on normal tissue, including proctitis, enteritis, and cystitis. These effects are generally acceptable and reversible but may be chronic; they are rarely sufficiently severe to require corrective surgical intervention. Other complications include occasional urethral stricture formation in patients who have undergone a previous transurethral resection of the prostate. Potency is preserved with definitive radiation therapy in the majority of patients but may diminish over time. Morbidity can be minimized by the use of sophisticated irradiation techniques, including the use of linear accelerators producing high-energy x-ray beams, careful treatment planning including simulation, and individualized shielding.

The assessment of local control is critical in evaluation of the results of radiation therapy. Reported rates of local tumor control are a function of the diagnostic method used to establish them. By clinical criteria alone, the local control rates are higher than if postirradiation positive biopsies are used as the end point. The likelihood of finding histologically positive biopsies following radiation therapy is of concern to physicians and is related to the clinical disease stage. The significance of this currently is being studied, but it may be predictive of subsequent distant relapse.

Survival is related to the initial clinical stage and histologic grade. The 10-year crude survival rates of patients with low-stage disease (A2 or B) treated with radiation therapy are equivalent to the expected survival of men in the comparable age groups. Survival rates in more locally advanced stages of disease clearly reflect the increased incidence of cancer death.

Should definitive radiation therapy, hormone therapy, and/or chemotherapy be used as adjuvant treatment in high-risk patients?

No data are available to support the routine use of adjuvant therapy after definitive surgery or irradiation. Preliminary data suggest that adjuvant hormone manipulation and irradiation deserve further study in locally advanced prostate cancer patients. A definition of the appropriate patient population for such studies remains to be developed.

What directions for future research are indicated?

The Consensus Development Conference on the Management of Clinically Localized Prostate Cancer provided a large body of information to optimize the diagnosis, staging, and management of this prevalent disease. Whereas many controversies were addressed, numerous questions were identified that await answers and thus serve as the focus for future research directions. These issues will require the collaborative input of investigators from both clinical and basic disciplines. As outlined in the consensus statement, many questions are being answered currently; others will be the focus for future research.

Directions for Clinical Research

- 1) Agree to a uniform classification and schema for histologic and cytologic grading, disease staging, and response criteria that are acceptable to health care professionals caring for patients with prostate cancer.
- 2) Define the appropriate use of diagnostic imaging in staging prostate cancer patients through well-designed, controlled comparison studies. The development of imaging methods to measure tumor volume could provide a noninvasive predictor of the aggressiveness of cancer.
- 3) Encourage educational programs for pathologists and cytologists in the diagnosis of prostate cancer with the purpose of increasing accuracy and uniformity.
- 4) Assess the availability and quality of surgical treatment and initiate surgical educational programs as needed.
- 5) Accept a uniform method for data reporting and statistical analyses that will allow meaningful comparisons of treatment results reported by various disciplines.
- 6) Identify clinical and pathologic prognostic variables. The identification of low- and high-risk features may allow more appropriate selection of treatments for patients with clinically localized disease. Parameters to study may include morphologic predictors, the correlation of DNA flow cytometry, prostate-specific antigen determination, and tumor cytogenetics with disease outcome.
- 7) Assess the clinical significance of positive postirradiation biopsies and identify ways to reduce the incidence of these positive biopsies.
- 8) Assess in controlled trials the role of localized postoperative irradiation in patients with positive margins after radical prostatectomy.

- 9) Assess in controlled trials the role of adjuvant hormonal therapy in patients with locally advanced disease after radical prostatectomy and/or definitive radiation therapy.
- 10) Clarify the clinical significance and therapeutic implications of the extent of nodal involvement.
- 11) Address the influence of treatment programs on the quality of life of patients and their loved ones. Identify appropriate psychosocial and psychosexual instruments and end points to assess quantitatively the effect of treatment in patients with both localized and metastatic disease. Study and implement innovative interventions to improve the psychological outcome.
- 12) Agree on a uniform clinical and pathologic definition of stage A1 prostate cancer. Initiate studies to define the natural history of untreated stage A1 patients to help determine which patients may benefit from treatment.

Directions for Basic Research

- 1) Encourage basic research to elucidate fundamental processes regulating normal prostate and prostate cancer growth and their impact on the natural history of disease.
- 2) Assess the diagnostic and therapeutic role of prostate cancer-specific monoclonal antibodies.

CONCLUSIONS

Radical prostatectomy and radiation therapy are clearly effective forms of treatment in physicians' attempts to cure tumors limited to the prostate for appropriately selected patients. Comparisons across studies suggest comparable 10-year survival rates with either form of management. What remains unclear is the relative merit of each in producing lifelong freedom from cancer recurrence. It is known

that traditional radical prostatectomy can provide 15-year cancer-free survival in appropriately selected patients that is equivalent to that of a comparably aged control population. On the other hand, sufficient long-term follow-up does not exist to permit a conclusion about the ability of radiation therapy to eradicate such cancer in an equivalent proportion of patients.

After appropriate primary irradiation, the long-term complication rate is now well defined and appears acceptable. The new approach to prostatectomy is clearly associated with a reduction in postoperative impotence. The true comparative incidence of impotence over time, however, awaits prospective evaluation. Although impotence may result from the alteration of normal anatomy, the psychological considerations should not be overlooked. Sexual rehabilitation should address both medical and psychological needs.

Information that a patient should have available when considering with his physician the choice of treatment includes:

- 1) probability of cure, mortality, complications, and other side effects of radical prostatectomy and radiation therapy;
- 2) risk of impotence and incontinence for either treatment;
- 3) psychosocial consequences of either choice;
- 4) extent and risk of pretreatment staging assessment tests; and
- 5) economic consequences of each form of treatment.

As competing, non-cancer-related causes of death (e.g., cardiovascular disease) may be expected to decrease for men over the age of 50, the issue of cure will become more important in low-stage disease. Properly designed and completed randomized trials that evaluate both disease control and quality of life after modern radiation therapy compared with radical prostatectomy are essential.

Overview: Historical and Contemporary

Willet F. Whitmore, Jr.¹

ABSTRACT—Recognition of the clinical importance of prostate cancer undoubtedly was delayed by the failure of clinicians or pathologists to distinguish consistently between benign and malignant prostatic growths until well into the 19th century. White used castration for prostatic enlargements in 1895, but Huggins and Hodges first placed endocrine therapy on a rational basis in 1941. Although a number of surgeons had attempted excision of prostate cancer, Young is credited with planning and performing the first radical perineal prostatectomy in 1904. Orthovoltage irradiation and various techniques of interstitial and intracavitary radium therapy were used in the treatment of prostate cancer early in the 20th century, but it was the development of megavoltage irradiation that reopened the door to the exploration of irradiation for localized prostate cancer following World War II. Endocrine manipulation, surgery, and irradiation remain the keystones of treatment. The management of prostate cancer is controversial for several reasons: 1) The disease occurs in an age range in which competing causes of mortality are high. 2) The natural evolution of the disease is varied, often long, and not consistently predictable. 3) Long-term survival has been reported for each of the principal modes of therapy, but randomized controlled studies have been limited. Uniformity in histologic grading, clinical staging, and evaluation of response to treatment would improve the quality of the data. Predictions of host life expectancy, tumor growth rate, metastatic potential, and tumor responsiveness to irradiation and endocrine therapy would enhance the rationale of treatment.—NCI Monogr 7:7-11, 1988.

This overview of prostate cancer is intended to provide a brief historical background, the major bases for uncertainties regarding management, some generalizations relative to treatment, resultant pertinent questions, some probable needs for clarifying current issues, and some tentative conclusions.

HISTORICAL BACKGROUND

For a neoplasm as common and as important as it has proved to be, prostate cancer has been slow to achieve the attention it deserves. Some historical landmarks help to place the contemporary picture in perspective. Although the Ebers papyrus from 1500 BC (1) suggests that prostatism was recognized as a problem in the aging male, distinctions between benign and malignant prostatic enlargements were rarely made, either by clinicians or by pathologists, until the 19th century. Langstaff [cited in (2)] in 1817 may have been the first to report an authentic case of prostate carcinoma. However, the infrequency with which the disease was recognized is suggested by Tanchon's [cited in (2)] review of 8,289 cancer deaths in Paris, France, between 1830 and 1840; only 5 cases involved the prostate. In 1898, Al-

barran and Halle [cited in (2)] demonstrated the frequency of the disease in reporting carcinoma in 14 of 100 prostatic enlargements. The independent and simultaneous publications of Rich (3) and Moore (4) in 1935 called the attention of clinicians and pathologists to the high prevalence of prostate cancer demonstrated by autopsy reports.

Relative to surgical treatment, Kuchler (5) in 1866 and Billroth [cited in (2)] in 1867 attempted perineal excisions of prostate cancers, and Kuster [cited in (2)] in 1891 used cystoprostatectomy and ureterointestinal diversion for a locally extensive prostate neoplasm. Despite these and other pioneering surgical ventures, it remained for Young [cited in (2)] to develop systematically and then perform radical perineal prostatectomy. Dr. Hugh Young first performed the operation on April 7, 1904, assisted by Dr. William Halsted, who may be credited with having inspired Young's efforts. The development of surgical excision for localized disease was a milestone. Radical perineal prostatectomy, however, was never widely performed. Patients meeting the appropriate selection criteria were rare, and few urologists became sufficiently adept to be comfortable with the procedure. Impotence was a usual sequel, urinary incontinence was not uncommon, and rectal injury was a formidable possible complication. Furthermore, irradiation and endocrine therapy later developed as alternative forms of treatment.

With the description of the retropubic approach to the prostate by Millin (6) in 1945, interest in total prostatectomy was renewed. The problems of impotence, urinary incontinence, and possible rectal injury remained, but the familiarity of urologists with suprapubic exposures assured a wider use of the procedure than had been afforded the perineal operation. When the anatomic dissections of Walsh and Donker (7) in 1982 appeared to unravel the mystery of the impotence associated with total prostatectomy, Walsh and his associates (8) in 1983 introduced modifications in the operative technique that led not only to a high probability of preservation of sexual potency but also to a more systematic and controlled operation that restimulated the interests of clinicians in the surgical control of localized prostate cancer.

Lymph node metastasis warrants special comment. Kocher [cited in (2)] operated for lumbar lymph node metastasis in a patient with prostate cancer in 1882, and Pasteau [cited in (2)] gave a remarkably complete and accurate description of the lymph node drainage of the prostate in 1897. In 1925, on the basis of the review of a large Mayo Clinic experience with prostate cancer, Bumpus (9) concluded: "... the lymphatic system is without doubt the earliest and most frequent site of metastatic lesions. ...". Despite these and other evidences of the familiarity of clinicians and pathologists with the occurrence of lymph node metastasis from prostate cancer, few surgical efforts have

¹ Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

been directed toward the control of such metastasis. Halsted's perception of female breast cancer was of a primary tumor possibly involving the regional lymph nodes of the supraclavicular fossa and axilla but still a potentially locoregional process. He designed radical mastectomy to encompass and possibly cure such lesions. Young's perception of prostate cancer was of a local lesion potentially involving the prostate and adjacent seminal vesicles. Although he would have been aware of the possibility of lymphatic dissemination, the regional lymph nodes were clinically occult and clinical staging procedures for their evaluation were nonexistent. The radical prostatectomy he designed was aimed at primary tumor control and possible cure. The policies regarding the regional lymph nodes that were formulated by surgeons treating breast cancer and by urologists treating prostate cancer may have been imprinted by these respective pioneers. It has been difficult to orient breast cancer surgeons toward the concept that regional lymph node metastasis implies systemic dissemination or urologic surgeons toward the concept that regional lymph node involvement may be consistent with still curable locoregional disease. One may speculate that the initial perceptions of Halsted and Young were instrumental in orienting these diametrically opposed treatment philosophies.

The use of x-rays and radium in the treatment of cancers followed shortly after the respective discoveries of Roentgen in 1895 and of the Curies in 1903. Loumeau in 1907 cited the use of x-rays, and Minet in 1908 and Pasteau, Wickham, and Degrais in 1910 [all as cited in (2)] used intraurethral radium to treat prostate neoplasms. The development of megavoltage irradiation during the 1940s made feasible the accurate delivery of sufficiently high radiation doses to stimulate the systematic investigation of external-beam irradiation in the treatment of prostate cancer, which is epitomized by the studies of Bagshaw and Kaplan (10) in 1962 and Budhraj and Anderson (11) in 1964.

In 1952, Flocks and his associates (12) combined surgery and the injection of colloidal ^{198}Au in the treatment of selected patients. This was the forerunner of explorations of brachytherapy with such radionuclides as ^{198}Au , ^{125}I , and ^{192}Ir .

Although White [cited in (2)] used castration in the treatment of prostatic enlargements in 1893, this approach was abandoned by surgeons in the 1920s because of unconvincing benefit from the procedure, failure to distinguish benign from malignant prostatic enlargements, and progressive evolution of therapeutic alternatives. It remained for Huggins and Hodges (13) in 1941 to establish the rationale and demonstrate the effectiveness of endocrine therapy in the management of advanced prostate cancer.

Surgery, irradiation, and endocrine therapy, either alone or in various combinations, remain the principal current methods of prostate cancer therapy.

BASES FOR UNCERTAINTIES

Current uncertainties in the management of localized prostate cancer may be justly credited to several considerations:

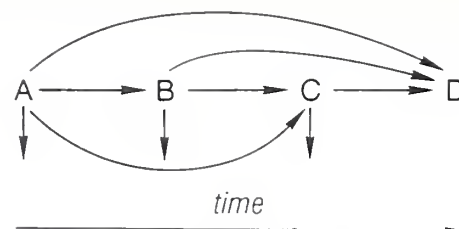


FIGURE 1.—Possibilities in stage progression.

1) One factor is the rapidly increasing clinical incidence of the disease after the age of 50 years, a time when there is a progressively rising risk of death from other causes. This makes "quality survival" a legitimate alternative to "cure" in selected patients with prostate cancer. Growing older is invariably fatal; prostate cancer is only sometimes so!

2) An important consideration is the varied and unpredictable natural evolution of the disease (fig. 1), which accounts for various possible rates and patterns of local and metastatic disease progression (14). The Patterns of Care Study of the American College of Surgeons (15) has yielded specific estimates of the contemporary relative frequency of occurrence of the various stages of prostate cancer. Experience with regional lymphadenectomy in patients with stages A, B, and C prostate cancer has provided what may be considered *minimal* estimates of the metastatic state associated with each of the respective local tumor categories (16). Nevertheless, for an individual patient with clinical stage A, B, or C prostate cancer, the rate and pattern of local and/or distant disease progression are imprecisely predictable. The earlier the stage of the neoplasm, the greater the number of possibilities in stage progression and the greater the number of treatment options, and in the absence of controls, the more difficult the assessment of the contribution of therapy to the end result.

3) Another uncertainty relates to inaccuracies in clinical staging. Clinical methods for defining the pathologic extent of the neoplasm have progressed enormously but remain short of ideal. In Young's early experience with radical prostatectomy, suitability for the operation was largely determined by history, a careful digital rectal palpation of the prostate, perhaps cystoscopy, and possibly a poor-quality radiograph. Continual refinements in clinical staging have occurred since that time (fig. 2). The resultant impact on case selection and on the potential for stage migration require no elaboration.

4) There is also a lack of uniformity in histologic grading, in clinical staging procedures and classification, and in criteria for assessment of response to treatment.

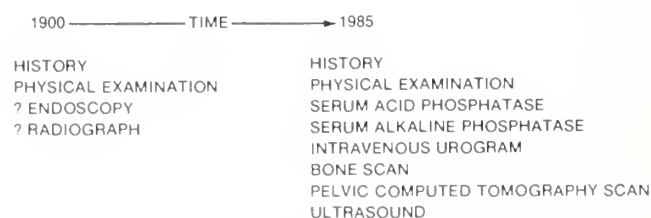


FIGURE 2.—Clinical staging for localized prostate cancer.

5) A final factor is the multiplicity of treatments, all inadequately controlled and applied differently to variously selected patients, often with incomplete assessment of the impact on the quality of life.

TREATMENT GENERALIZATIONS

Appropriate treatment implies that therapy is not applied if it is unnecessary or if it will be ineffective and will decrease qualitative enjoyment of predicted life expectancy. For patients with stage A prostate cancer, the usually protracted tumor evolution and the competing mortality from other causes provide uncertain bases for categorical treatment. Although all stages B, C, and D cancers must originate from stage A lesions, the vast majority of stage A neoplasms remain so throughout the lifetime of the host. Epstein et al. (17) and Blute and associates (18) have recently confirmed the lethal potential of some clinically identified stage A lesions but have simultaneously illustrated the far greater probability of death from other causes in these respective experiences.

Categorical treatment of all clinically identified stage A lesions would undoubtedly constitute therapeutic "overkill." Predictability of both the biologic potential of such a tumor and the life expectancy of its host is an ultimate requirement for rational treatment recommendations and constitutes a more urgent objective than does earlier diagnosis of such lesions (19). Furthermore, the specific effectiveness of the current treatment armamentarium in patients with stage A prostate cancers has yet to be established by clinical experience.

For selected patients with stage B prostate cancers, there are gross similarities in clinical local control and overall 10- and 15-year survival rates following either external-beam irradiation (20-23) or surgical excision (24,25). The possible persistence of locally positive biopsy specimens and the variable use of endocrine therapy in such radiation therapy experiences suggest that a great proportion of patients treated by surgical excision may actually be free of neoplasm at 15 years but simultaneously suggest that the overall survival advantage of cure at 15 years is, at best, small.

Current information does not exclude a possibly significant survival advantage of a particular treatment after 15 years, but the age range of the prostate cancer population and competing causes of mortality suggest that the relevance of cure of this neoplasm to survival per se will progressively diminish as follow-up intervals become longer.

Apparent cures, disregarding variation in definitions, have followed external-beam irradiation, surgical excision, interstitial irradiation (26), and even endocrine therapy (27-30). Whether the subsets of patients cured following different treatments are identical is unknown, but the salvage by irradiation following local failure after surgery (31) and the salvage by surgery following local failure after irradiation (32) suggest that the subsets may be at least partially different.

If one considers the frequency with which a watchful waiting course has probably been applied in the management of stage B prostate cancer, there is a dearth of information on the subject. Endocrine therapy usually has been administered for disease progression in such circum-

stances. Limited evidence (27,28,33,34) suggests that, in such patients, overall 15-year survival rates (*not* based on no evidence of disease) are grossly similar to those achieved in apparently comparable patients managed by radical excision or irradiation. Data concerning rates of local and distant disease progression in patients with stage B cancer managed either by watchful waiting or by endocrine therapy are extremely limited (34), and quality-of-life issues with patients so managed remain to be addressed.

For stage C prostate cancer, external-beam irradiation or endocrine therapy has been the most common treatment, but a convincing survival or local control advantage to either approach is lacking (21,22,35,36). Irradiation, surgery, or endocrine therapy has been useful for local control in some patients who have failed alternative treatment, but the relative effectiveness of the different management options in various circumstances is unclear. Various selected patients have received the following forms of treatment with some apparent clinical success: radical prostatectomy (37), cystoprostatectomy with lymph node dissection (38-41), endocrine therapy followed by radical prostatectomy (42), radical prostatectomy with lymph node dissection and endocrine therapy (43,44), interstitial irradiation with lymph node dissection (26), and radical excision with interstitial irradiation, lymph node dissection, and endocrine therapy (45,46). Lack of control data, varied selection criteria, frequent use of endocrine therapy, and inconsistent response criteria confound interpretations.

QUESTIONS

The foregoing considerations justify the following pertinent questions:

1) Is cure necessary? Although many more die with prostate cancer than of it, the need for cure is amply demonstrated by the significant mortality from the disease.

2) Is cure possible? On the basis of 15-year survival without evidence of neoplasm after treatment of selected stage B prostate cancers by surgical excision or irradiation, the answer is a qualified yes. There is evidence that such survival per se must be considered to be a *qualified* indication of cure. This evidence includes: local or distant recurrence first recognized 15 or more years after local treatment (47), grossly similar 15-year survival rates following watchful waiting with endocrine therapy if necessary, and grossly similar 10- to 15-year survival rates after either surgical excision or irradiation with variable supplemental endocrine therapy.

3) Is cure necessary in those for whom it is possible? This question is derived primarily from the grossly similar 10- to 15-year survival rates in selected patients with stage B cancer following management by watchful waiting variably supplemented with endocrine therapy, by radical excision, or by radiation therapy variably supplemented with endocrine therapy. No definitive answer to this question is currently possible.

4) Is cure possible in those for whom it is necessary? This question derives from the weakness of the evidence that therapy has diminished mortality from prostate cancer and from the persistently poor prognosis associated with tumors of high grade and those with regional lymph node

metastasis. No definitive answer to this question is currently possible.

POSSIBILITIES FOR CLARIFICATION

Efforts to answer unresolved questions encourage two simply stated, although not simply accomplished, considerations. These are:

- 1) standardization and adoption of uniform criteria for the pathologic characterization, clinical staging, and for assessment of responses to treatment; and
- 2) appropriate randomized clinical trials and/or identification of tumor-host features that constitute reliable predictors of growth rate, metastatic potential, and responsiveness to a specific form of treatment.

CONCLUSIONS

The end result in the patient with prostate cancer may be considered a combined consequence of host natural history, tumor behavior, and treatment effectiveness. In the absence of controlled studies or reliable predictors of either host or tumor behavior, the relative impacts of specific therapies on tumor control and survival remain ambiguous. The possibility that the long survival after treatment is more a consequence of the natural behavior of the disease than of the nature and consequences of the treatment is one with which surgical and radiation oncologists currently must live. Quite apart from the uncertain contribution of various treatments to cancer cure, local control is a realistic and useful treatment objective. The relative efficiencies of different methods of treatment, including endocrine therapy, in attaining this limited objective are in need of additional study, which should incorporate further attention to treatment impact on the quality of life.

There is logically no *best* method of treatment for *all* patients, but rather a variety of methods, one of which is best for a particular patient and his particular tumor. Furthermore, the best treatment for the cancer may not necessarily be the best treatment for the patient. The challenge for physicians is to identify features in the individual host-tumor setting that indicate the need for and specify the optimal method of management.

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I. Staging

Histologic Grade, Clinical Stage, and Patient Age in Prostate Cancer

Donald F. Gleason^{1,*}

ABSTRACT—The highly variable and often prolonged clinical course of prostate cancer poses difficult problems. Some patients appear to be at such low risk that overtreatment should be avoided. Many patients must be studied for many years before 2 treatments can be compared. If the patients could be sorted into groups with predictably different survival rates, such studies could be completed in less time and/or with fewer patients. Accumulated experience indicates that the survival rates for patients with a diagnosis of prostate cancer are determined largely by three factors: the clinical stage, histologic grade of the tumor, and the patient's age. Treatment is a fourth variable factor that requires further study. In this paper, the relationships and interactions among grade, stage, and age are analyzed and discussed, and ways are suggested in which they can be combined to enhance stratification and discrimination in clinical trials of treatment. The information can also be applied broadly to the management of individual patients, but it is painfully obvious that we need a much larger body of accumulated treatment data that must include more uniform clinical staging, uniform histologic grading, and detailed patient-age reporting. These data would help adjust for the nonuniform mixture of patients in different studies. The problem of variable patient selection processes before admission to a study affects the results of many reported studies and remains a difficult problem.—NCI Monogr 7:15–18, 1988.

THE PROBLEM

The variable and often prolonged clinical course of prostate cancer poses a severe challenge: Many patients must be studied for many years so that 2 treatments can be compared. Some patients with stages A and B cancers, diagnosed early, appear to live out their normal life span and die of other causes or conditions. Recent reports remind us that some patients with stage A tumors do progress to death from cancer, but these are almost always those with less differentiated tumors. The fact remains that only 2%–10% of patients with stage A tumors die of cancer, as proved in various series of studies (1). Stage B tumors are, on the average, larger and more aggressive, but there is also substantial overlap with stage A in this regard.

Some simple autopsy statistics emphasize the problem. Careful examination of the entire prostate at autopsy reveals that a surprising incidence of unsuspected carcinomas begins when patients are about 40 years old and increases steadily with age. If the incidence of these cancers is about 10% at age 55, 20% at age 65, and 30% at age 75, then

two-thirds of the tumors found in the 75-year-old men must have been present for more than 10 years and one-third must have been present for more than 20 years! The actual incidence does not affect these conclusions, which depend only on the increasing incidence with age (fig. 1).

Most of these tumors found at autopsy are small and well differentiated. They obviously caused no difficulty and would presumably have remained "silent" for many more years. They apparently were not serious threats to the health of the patients, but some of these tumors will inevitably be found in prostate tissue removed during life for presumed benign obstruction and then they do become management problems.

The question is: Can we distinguish those tumors which grow very slowly from those which grow more rapidly and thereby avoid unnecessary and potentially harmful treatment? Histologic grading offers a partial solution to that question.

HISTOLOGIC GRADING

Prostate cancer also displays a wide range of histologic appearances, and many have reported strong correlations between histologic and biologic malignancy, as with many other cancers. Well-differentiated tumors grow slowly; poorly differentiated tumors grow rapidly.

The VA ("Gleason") grading system is standardized by a drawing (2,3) that facilitates adoption by other workers. The drawing identifies 5 grades of tumor, but 2 grades are often present in 1 patient. The 2 grade numbers are added together to create a histologic score, which can range from 2 to 10. (For pure single-grade tumors, the grade number is doubled.)

In the VACURG studies, the histologic score in the original diagnostic biopsy was the most powerful single correlate with subsequently observed measures of biologic malignancy (2–4). It was strongly correlated with the subsequently observed cancer death rates (fig. 2) and was also correlated with the initial clinical findings, such as the extent of tumor, the presence of hydronephrosis, elevation of serum acid phosphatase, etc. In addition, the histologic score correlated with the rate of progression from the initial clinical stage to higher stages (4) and with the incidence and extent of metastases at autopsy years later.

Other workers confirmed the reproducibility of the VA grades (5) and confirmed and extended the histologic and biologic correlations (6–9). Some (7–9) even suggested that the correlation with lymph node metastases at exploratory laparotomy was strong enough to consider foregoing the risks of staging lymphadenectomy in patients with the highest and lowest histologic scores. Thomas et al. (10) documented a sharp increase in the incidence of "upstaging"

ABBREVIATIONS: VA = Veterans Administration; VACURG = Veterans Administration Cooperative Urological Research Group.

¹ Department of Laboratory Medicine and Pathology, University of Minnesota School of Medicine, Minneapolis, MN.

* Reprint requests to: Donald F. Gleason, M.D., Ph.D., 6211 Logan Ave., S., Minneapolis, MN 55423.

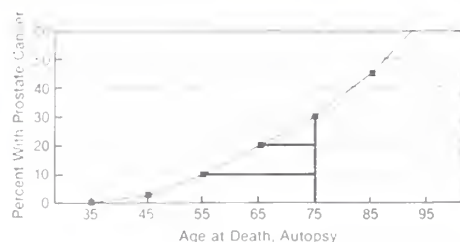


FIGURE 1.—Approximate incidence of prostate cancers found at autopsy at various ages. Note that one-third of the tumors in the 75-yr-old men had been present more than 20 yr!

(the finding of unexpected extension of tumor outside the prostate at laparotomy for prostatectomy) between histologic scores 6 and 7 in the initial biopsies of 130 clinical stages A and B patients (fig. 3).

The separation of patients into groups with predictable degrees of malignancy should facilitate retrospective comparison of treatments and optimize the prospective randomization of treatments. Use of histologic grade can assist in the management and treatment decisions for individual patients.

CLINICAL STAGE

Other initially observed parameters also correlate well with the subsequent course of prostate cancer, including tumor size, seminal vesicle invasion, extension through the capsule, lymph node metastases, distant metastases, elevated serum acid phosphatase, etc. Various combinations of these findings are used by physicians to define the clinical stages, which also correlate strongly with the subsequent clinical course.

It is worth emphasizing that all of these parameters, including the histologic score, are obviously correlated broadly with the degree of biologic malignancy of the tumors. The clinical parameters have the quality of "mileposts" which indicate *how far* the tumor has progressed along its course. The histologic grade appears to be more directly related to the specific abnormalities at the molecular-genetic level that control the histologic structure and function of the tumor cells and is strongly correlated with the *rate* at which the tumors grow and progress.

The clinical stage appears to be the product of the innate degree of malignancy of the tumor and the duration of the tumor (unknown) before diagnosis. Four clinical stages are usually defined at the time of the initial diagnosis, commonly labeled A, B, C, and D or I, II, III, and IV in

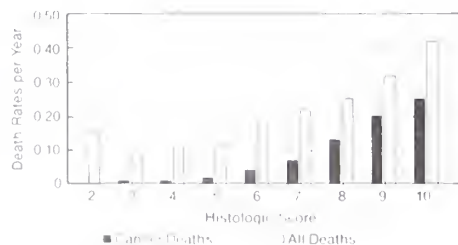


FIGURE 2.—Histologic scores (primary plus secondary grades) vs. cancer-specific and total death rates.

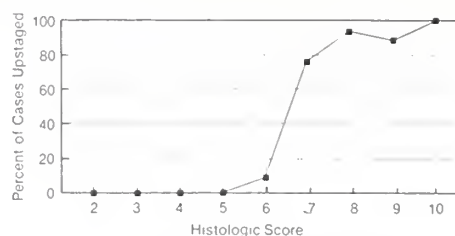


FIGURE 3.—Percent of 130 clinical stages A and B patients upstaged to stage C or D at attempted prostatectomy. Note sharp increase between histologic scores 6 and 7. Graph drawn from data of Thomas et al. (10).

different studies. The VA studies used the simple, numbered clinical stages of that time:

- Stage I: No palpable tumor, no evidence of metastases.
- Stage II: Palpable, localized nodule, no known metastases.
- Stage III: Palpably extended tumor, no known metastases.
- Stage IV: Metastases present and/or elevated prostatic serum acid phosphatase.

Tumors first diagnosed in stage III (C) progress more rapidly than stage I (A) and II (B) tumors because, on the average, not only are they a higher grade but also time elapsed while they were (unrecognized) in stage I (A) and/or II (B), i.e., lead time bias. Stage IV (D) tumors progress more rapidly than do stage III (C) tumors for similar reasons.

The histologic score and the clinical stage showed partial correlation with each other in the VA data, as would be expected, with more low-grade tumors in the lower stages and more high-grade tumors in the higher stages. However, almost all the histologic grades can be found in all the clinical stages, and both stage and grade also had strong independent predictive correlations with the biologic malignancy of the tumors. When these correlations were combined, simple addition of the score number to the stage number (with a weighted value of 5 for stage IV) gave a powerful new stage-grade category number that could range from 3 to 15 and was strongly correlated with the subsequent cancer death rates (fig. 4).

This category combines the clinical stage and histologic grade into a single numerical expression of the risk of progression and cancer death for patients with that same category score. It consolidates the overlapping similar clinical courses of the patients with lower stages and higher

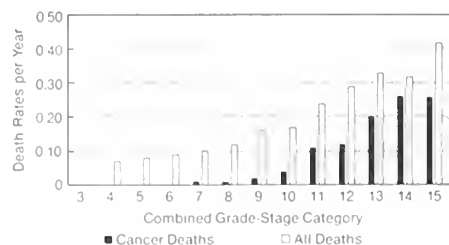


FIGURE 4.—Combined clinical stage-histologic grade category vs. cancer-specific and total death rates.

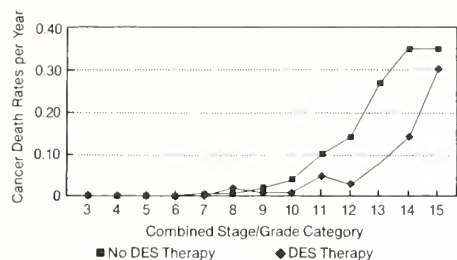


FIGURE 5.—Reduction of cancer death by treatment with diethylstilbestrol (DES) above stage-grade category 8 but no detectable effect below category 9.

grades and those with higher stages and lower grades. Also, it provided a useful categorization of the patients in the VACURG studies who did or did not benefit from treatment with diethylstilbestrol (fig. 5).

This combined stage-grade category was largely ignored in the literature on the prostate because of the enthusiasm for the subdivided clinical stages introduced by Jewett (A1, A2, B1, B2, etc.). In that system, the histologic grade appears only in substage A2 (defined as more than a certain amount of tumor or poorly differentiated tumor). The combined stage-grade category always incorporates the histologic differentiation of the tumor. Its value was recently tested and reaffirmed by the group at Memorial Sloan-Kettering Cancer Center (11).

PATIENT AGE AT DIAGNOSIS

Finally, it is easy for physicians to overlook one of the most powerful predictors of any survival curve, the age of the patient. Other factors being equal, a group of older men will die sooner than a group of younger men. After age 50, the changes per decade in the normal death rate are as great as or greater than the changes related to tumor stage and grade (fig. 6).

Survival after diagnosis appears to depend largely on three factors: the histologic grade, clinical stage, and age of the patient. The effect of treatment is a fourth variable factor.

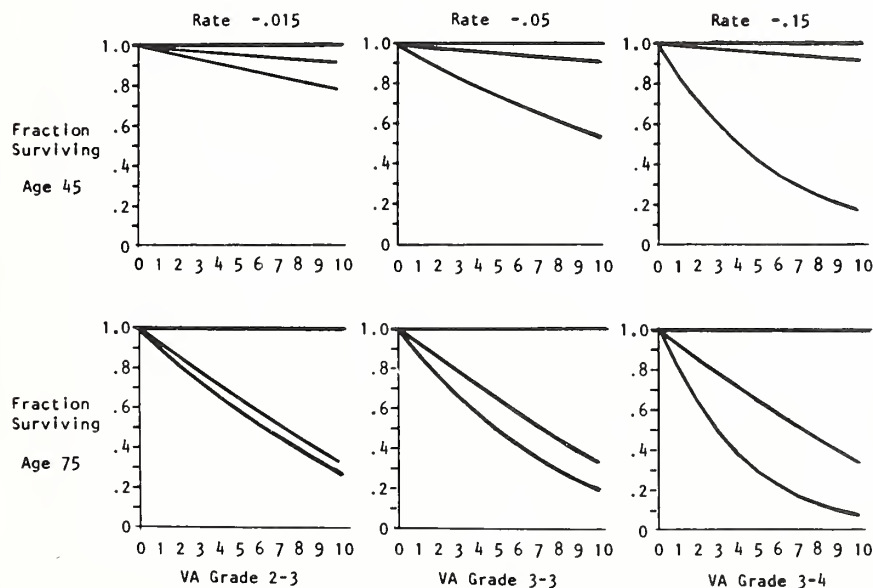


FIGURE 7.—Survival curves showing effect of three grades of prostate cancer on survival for 45-yr and 75-yr-old men. Upper curve in each graph is the normal survival curve for the age group (DHEW data for United States white males, 1969-71). Lower curve is the same normal survival curve reduced by the cancer-specific death rate associated with tumors of VA histologic scores 5, 6, and 7.

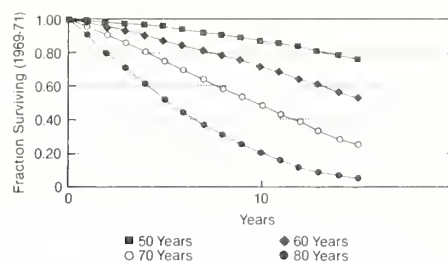


FIGURE 6.—Normal survival rates for men of specific ages (DHEW mortality data of 1969-71 for white United States males).

Published actuarial survival data like those in figure 6 can be combined mathematically with the cancer-specific death rate for a certain tumor grade and/or stage to produce a theoretically predicted survival curve for a group of such patients. The decrease in life expectancy can be calculated. Examples (combining only age and grade for simplicity) are shown in figure 7. They could be used in patient-doctor discussions of prognosis and therapy. Series of such theoretical curves provide a mathematical model for some of our intuitive ideas about balancing stage, grade, and age for patient management considerations. For example, it is apparent from figure 7 that grade 2+3 tumor in a 75-year-old man does not increase his mortality rate drastically, but the same tumor in a 45-year-old doubles his mortality rate. Grade 3+4 tumor will be associated with an ominous prognosis at any age.

Calculation of the effects on the mortality rate could be used to help select the most appropriate treatment for groups of patients defined by age, stage, and grade. However, the decision points are not defined by the numbers themselves. Additional carefully accumulated data and experience would be required to help the physician decide if a 10% or 20% or 30% change in the death rate is enough to select treatment A over treatment B, for example.

Finally, the general state of health and the opinions of the patient and his physician on the cost/benefit ratio of the risks and side effects of each treatment to the possible

increases in survival will always enter into those choices. Those difficult value judgments will always remain, but mathematical analysis of the effects of histologic grade, clinical stage, and patient's age may narrow some of the difficult areas.

SUMMARY

Uniform histologic grading, clinical staging, and patient-age reporting appear essential for further progress in the management and treatment of prostate cancer to facilitate impartial comparison of the results of various clinical studies with the use of the correlations described herein.

ADDENDUM

It is imperative, in applying the VA grading system, that one record both histologic **grades** and histologic **score**:

"The tumor is grade 3 and 4, score 7," or

"The tumor is pure grade 3, histologic score 6."

The unqualified numbers 2, 3, 4, or 5 might be the histologic scores of several well-differentiated prostate tumors, but they might also be the histologic grades of 1 well-differentiated, 1 moderately differentiated, and 2 poorly differentiated tumors, and thereby present possibly disastrous misunderstandings.

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Fine-needle Aspiration of the Prostate

Mitchell C. Benson^{1,2}

ABSTRACT—Fine-needle aspiration biopsy of the prostate has been used for over 20 years as the prostate biopsy technique of choice throughout much of Europe. However, this technique has only recently gained acceptance in the United States. There is now an enlarging body of data confirming that fine-needle aspiration can be viewed as a safe, accurate, and reliable means for detection and diagnosis of prostate cancer. This review summarizes the European and United States experience with fine-needle aspiration and supports the utility of this biopsy technique as an important addition to the urologist's diagnostic armamentarium.—NCI Monogr 7:19-24, 1988.

Despite widespread use of transrectal aspiration biopsy of the prostate throughout Europe, this technique is only slowly gaining acceptance by urologists as a safe, reliable, and accurate means of detecting prostate cancer in the United States (1-13). It appears that lack of experience with the technique on the part of the urologist and pathologist is at the root of this inertia. Thus the purposes of our presentation are to 1) discuss the technique of aspiration biopsy, 2) review the European and American experience, and 3) project the role this technique will play in the diagnosis and treatment of prostate cancer.

Biopsy can be defined as the process of removing tissue from living patients for diagnostic examination. Prostate biopsy in the United States has traditionally been performed with instruments that remove a core or piece of tissue for histologic examination. This means that a portion of a tumor in its natural environment (epithelia, stroma, and vascular network) is removed, processed, and microscopically examined for the physician to establish a diagnosis. In addition, the tumor cells can be graded, and this results in our ability to prognosticate survival, though not necessarily in an individually predictive manner. Broders (14) was the first to point out that grade correlated with prognosis when he stated: "The time is not far distant when not only physicians but also the patients and their relatives as well as life insurance companies will be interested in the grade of malignancy of cancer. If a surgeon knows the grade of malignancy of a cancer in addition to its size and situation, he is certainly in a better position to render more efficient treatment, and a more accurate prognosis than one without such knowledge." This statement has certainly become true, and it points out that biopsy not only can establish a diagnosis but sometimes can be useful in directing therapy.

Finally, physicians can use biopsy results to monitor patient response to therapy. Changes caused by disease regression can be seen following radiation therapy and androgen withdrawal and in many cases are thought to be predictive of patient prognosis and duration of response (15-19).

Thus histologic biopsy is used by physicians to establish a diagnosis, direct therapy via predicting the aggressive nature of a tumor, and to monitor responses by assessing tumor persistence or recurrence after therapy. The following information should serve to prove that these same tasks can be accomplished with fine-needle aspiration.

TECHNIQUE

Although Franzen (1) was not the first to perform transrectal aspiration biopsy of the prostate, he was certainly the individual responsible for developing the apparatus currently in use. He described the use of a 22-gauge needle introduced into the prostate via the rectum. Although certain advances in instrumentation have made the technique easier to perform, the methods remain essentially unchanged.

The following materials are used: a 22-gauge disposable aspiration needle (Cook Urological, Inc., Spencer, IN); a 20-ml disposable Luer-Lok syringe (Becton Dickinson and Co., Rutherford, NJ); a needle guide (Cook Urological, Inc.); a pistol-grip syringe holder (Precision Dynamics Corp., San Francisco, CA, or Cook Urological, Inc.); sterile gloves; and microscope slides.

Inasmuch as the rectum contains no pain sensory nerves, transrectal aspiration of the prostate can be performed without the use of anesthesia. In general, the patient feels no more discomfort than is experienced during a rectal examination. Thus this procedure can be as safely and comfortably performed in the physician's office as in the operating or cystoscopy suite. No preaspiration antibiotics are necessary, but as with all urologic procedures, a urine culture should be checked before the procedure, and it must be sterile. No rectal preparation is required.

The patient is placed in the lithotomy position, and the prostate is palpated with the index finger. The examining glove is then removed and replaced with a sterile glove. The needle guide is placed on the index finger, and a sterile finger cot or glove is placed over the tip of the needle guide. Next the finger is reinserted into the rectum, and the tip of the needle guide is placed flush against the rectal mucosa below the prostatic induration. The disposable needle with the stylet in place is passed through the guide and into the prostate nodule. The stylet is then removed, and the 22-gauge needle is connected to the 20-ml syringe already in the pistol grip. The pistol grip allows for one-handed aspiration and manipulation of the needle. The apparatus is moved back and forth approximately 20 times while negative pressure is maintained on the needle. The negative

¹ Department of Urology, Columbia-Presbyterian Medical Center, 622 West 168th St., New York, NY 10032.

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pressure is released, and the needle is withdrawn from the prostate. The aspirated material is then deposited directly on a slide by injection of 10 ml air through the needle. If the aspiration must be repeated because there is insufficient material, a new needle need not be used if gloves were sterile because the Franzen needle is never in contact with the rectal contents. When air pressure alone is not sufficient to flush the syringe, the stylet can be replaced to clear the lumen and deposit the specimen on a slide. The slide is then smeared in a manner similar to that used in the preparation for a blood count. Some pathologists prefer the specimen to be air-dried, but others prefer an ethanol fixation. If ethanol fixation is used, the slides should be placed in the ethanol before drying takes place. Whether the specimen is air-dried or fixed, certain artifacts are introduced, so it is important that the pathologist's preference be ascertained. If the aspirated specimen is being used for other studies, it can be placed directly into Hanks' balanced salt solution or growth media.

INDICATIONS

The indications for performing a fine-needle aspiration of the prostate are the same as those for any biopsy technique. The only absolute indication is a palpable abnormality on rectal examination. Whether lesions perceived on ultrasonographic examination of the prostate should be biopsied is beyond the scope of this review.

As with all urologic procedures, an untreated urinary tract infection or acute prostatitis is a contraindication to biopsy. The procedure should also be deferred in patients with acute infectious rectal diseases.

RESULTS OF STUDIES

The most important issue regarding transrectal aspiration of the prostate is its degree of accuracy in diagnosing or excluding prostate cancer, i.e., sensitivity and specificity. Specificity is the probability of a negative test in a man who is free of the disease. Sensitivity is the likelihood of positive results in a patient with prostate cancer. However, one must review data carefully because no published series uses autopsy analysis as the standard. Therefore, when the results of perineal biopsy and aspiration biopsy differ, one must decide which is the true result. The result of the aspiration biopsy can be considered to be false positive, or the result of the perineal biopsy can be considered to be false negative, depending on the standard used.

The largest published series of cytologic diagnoses of prostate tumors presents reports on 1,430 biopsies in 1,110 patients reviewed by Esposti at the Karolinska Institute in Stockholm, Sweden (2). He indicates that about 10% of prostate cancers are not detected at the first aspiration biopsy, and this is in keeping with other reports. Table I demonstrates that in large series of aspirations (>100 performed), a sensitivity of 89%–91% can be achieved.

Prostate cancer is found to be responsible for approximately 50% of palpable abnormalities within the prostate as determined by standard biopsy techniques (histologic core biopsy). The presence of cancer was demonstrated in only 37% of the patients who had fine-needle aspiration biopsies. This lower rate of positivity should not be perceived as

TABLE I.—Sensitivity of fine-needle aspiration biopsy of the prostate in a large series^a

Reference	Aspirations	Carcinomas	Positive aspirations	Suspicious aspirations
(2)	162	60	54	3
(3)	100	45	34	5
(7)	433	198	157	1
(20)	469	203	197	10
(21)	182	50	37	NR
(22)	753	132	112	0
(23)	454	159	153	^b
(24)	350	214	205	^b
Total	2,903	1,061	949	19

^a NR = not reported. No. of positive aspirations/No. of carcinomas = 89%. No. of positive + suspicious aspirations/No. of carcinomas = 91%. No. of carcinomas/No. of biopsies = 37%.

^b Numbers are included in positive results.

lower sensitivity. It is probable that the clinicians are sampling extremely subtle differences in consistency because needle aspiration can be performed in the physician's office without anesthesia. This interpretation is supported by Esposti and Franzen (5), who report positive biopsies in only 1,410 of 4,630 aspirations or 30%. Their lower positivity rate is not secondary to missed lesions; rather, there are a larger number of true negatives.

The incidence of false-positive and false-negative biopsies needs to be addressed before fine-needle aspiration can be accepted as a reliable procedure. False-positive rates range between 0% and 2%. Clearly, false-positive results are of great concern, but as noted in the beginning, whether a result is a false or true positive depends on the reference standard. In 469 cases reported by Esposti (24), incidence was 0% when a positive aspiration was not confirmed at either autopsy or radical prostatectomy. Thus, with adequate experience, false-positive results should not occur.

Even though false-negative biopsies do not result in unnecessary procedures, they may result in harmful delays in the institution of therapy and thus are as serious as false-positive results. However, the Karolinska experience (5) demonstrates that most cancers are detected on repeat biopsy and that the sensitivity of aspiration biopsy in detecting cancer is equivalent to standard histologic core biopsy. Thus, with repeat aspiration when clinically indicated, the false-negative rate is less than 4% of the cases (5). The recommendation for patients with a palpable nodule, suspected to be prostate cancer but with a negative aspiration, is a repeat aspiration and/or a histologic biopsy.

Recently, reports on the American experience with transrectal aspiration have appeared in the literature (8–13). The experience indicates a learning curve during which aspiration samples may be inadequate for accurate interpretation. This learning curve is secondary to both the pathologist's need to gain experience at diagnosis and the urologist's need to learn how to obtain and prepare adequate material. In general, approximately 100 aspirations are necessary before the urologist consistently obtains high-quality samples. Therefore, it seems appropriate that initially aspirations be done in conjunction with whatever technique

the urologist usually performs. Each physician could then assess at what point performance of a standard biopsy is no longer warranted. When the aspiration biopsy is positive but the histologic biopsy is negative, both procedures should be repeated. If the discrepancy in results persists, the slides from the aspiration and standard biopsies should be sent to an independent pathologist with documented experience in the cytologic diagnosis of prostate cancer.

In excellent hands, 10% of prostate cancers are missed at first aspiration; this result is not different from that with standard histologic biopsies, which have similar false-negative results (11). When suspicious nodules continue to yield negative biopsies, ultrasound-guided biopsies could be performed if the lesion can be ultrasonographically identified. This would serve to document that the aspiration needle or biopsy needle is indeed in the nodule in question.

PATHOLOGIC ASSESSMENT

Experience is necessary for an accurate diagnosis with any biopsy sample. With aspiration biopsy, the pathologist often examines individual cells or clumps of cells out of their natural environment; thus a special expertise is necessary.

When false-positive reports are generated, they are most often secondary to the occurrence of atypical hyperplasia, squamous metaplasia, granulomatous prostatitis, or aspiration of the seminal vesicle (25). The reason for a false-negative interpretation is often secondary to the presence of well-differentiated cancer. To assist in the diagnosis of well-differentiated cancer, Kline and Kannan (26) have developed major and minor criteria for the cytologic interpretation of well-differentiated prostate cancer (table 2). They define five major and five minor criteria that are relatively unique to well-differentiated cancer as opposed to benign disease. They recommend systematic use of these 10 parameters to enhance diagnostic sensitivity and allow detection of well-differentiated cancer.

CYTOLOGIC VERSUS HISTOLOGIC GRADE

The importance of grading of prostate cancer is self-evident because grade certainly correlates with patient

TABLE 2.—Criteria for cytologic diagnosis of prostate cancer

Cytologic characteristic	Benign, %	Histology of cancer, % ^a	
		WD	MD to PD
Major criteria			
Cellularity	15	92	75
Dyshesion	0	48	95
Nuclear irregularity	0	64	90
Anisonucleosis	7	84	100
Macronucleoli	7	72	95
Minor criteria			
Polarity loss	4	68	95
Crowding	7	72	75
Piling	4	68	60
Microacini	0	60	35
Cell enlargement	4	80	75

^a WD = well-differentiated; MD = moderately differentiated; PD = poorly differentiated.

TABLE 3.—Correlation of cytologic and histologic grade in 100 patients with prostate cancer^a

Cytologic grade	Histology		
	WD	MD	PD
I	15	4	0
II	3	33	9
III	0	5	31

^a See table 2 for definitions. Results demonstrate a 79% exact correlation.

prognosis (27). Therefore, before aspiration cytology can be accepted as a diagnostic tool for prostate cancer that is equivalent to histology, it must be proved that the potential for prognostication with cytologic grade is similar to that with histologic grade.

In many instances during the inception of fine-needle aspiration, core biopsy and aspiration were performed simultaneously; therefore, data correlating histologic and cytologic grades are available (table 3). The results demonstrate a 79% exact correlation; in no instance were cytologic grade I cells deemed to be poorly differentiated histologically or grade III cells seen as well differentiated (3,28,29).

Cytologic grade can also be compared with Gleason score (table 4). There is a 75% correlation between the three cytologic grades and the Gleason sum when the Gleason sum is divided into three categories: 2–4, 5–7, and 8–10 [(12,30–32); unpublished data]. As with histologic grade, there were no instances when cytologic grade I cells demonstrated a Gleason sum of 8–10 or cytologic grade III cells yielded a Gleason sum of 2–4.

Cytologic grade not only correlates with histologic grade and Gleason score but also has a direct correlation with survival, as shown in tables 5 and 6 (28,33). In a series of 469 patients with minimum 5-year follow-up seen at the Karolinska Institute (table 5), survival was directly related to cytologic grade (28). As would be expected, the better differentiated tumors tended to be a lower stage; 47% of grade I tumors were stage B and only 10% were stage D. In distinction, only 10% of grade III tumors were stage B and 33% were stage D. No tumors in any category were stage A.

A similar study from the University of Munich, Federal Republic of Germany (33), reported on survival in 488 patients (table 6). Survival was related to cytologic grade, and more importantly, survival was determined relative to cancer-related death. These authors divided cytologic grade into four categories and grade was not correlated with stage. Table 6 demonstrates that 3- and 5-year survival rates correlated with cytologic grade and that the percentage

TABLE 4.—Correlation of cytologic grade and Gleason score in 149 patients with prostate cancer^a

Cytologic grade	Gleason score		
	2–4	5–7	8–10
I	15	11	0
II	3	58	17
III	0	6	39

^a Results demonstrate a 75% correlation.

TABLE 5.—Correlation of cytologic grade and percent survival of 469 patients with prostate cancer in a study at the Karolinska Institute^a

Cytologic grade	No. of patients	Percent survival at:				
		1 yr	2 yr	3 yr	4 yr	5 yr
I	131	89	84	73	70	68
II	265	87	75	61	58	55
III	73	73	45	29	15	11

^a Of the patients studied, 29% had stage B disease, 58% stage C, and 14% stage D (28).

of patients dying of prostate cancer also increased with increasing cytologic grade.

Thus, just as survival can be shown to correlate with histologic grade or Gleason sum, survival can also be shown to correlate directly with increasing cytologic grade. It appears that aspiration cytology has a prognostic value equivalent to that of histologic methods.

CYTOLOGIC MONITORING OF RESPONSE TO THERAPY

Hormonal Therapy

Core biopsies performed following castration or estrogen administration have previously been shown to demonstrate pyknotic nuclei and glycogen or squamoid histologic changes (19). These same findings have been seen in samples obtained by transrectal aspiration (4,34). In a study performed at the University of Umea, Sweden (34), aspiration biopsies have been performed at 12, 24, and 36 months to predict patient response to estrogen therapy (table 7). Cytologic findings following therapy were classified as showing disease regression or no change and were correlated with patient response at each biopsy interval. The results demonstrate that survival in patients with tumors showing disease regression is prolonged over survival in patients whose tumors do not show regressive changes. The results also suggest that disease progression can be seen on biopsy before it becomes clinically manifest.

Radiation Therapy

The necessity and significance of prostate biopsy after radiation therapy are discussed elsewhere and in this volume (15-18), but equally important is the fact that adequate postirradiation samples can be obtained by fine-needle aspiration (35). In a series of 66 patients treated with external-beam radiation therapy, 53 consented to a postir-

TABLE 6.—Correlation of cytologic grade and percent survival of 488 patients with prostate cancer in a study at the University of Munich^a

Cytologic grade	Percent survival at:		Percent deaths from prostate cancer
	3 yr	5 yr	
I	74	60	33
II	70	66	54
III	51	36	60
IV	37	37	94

^a See (33).

radiation aspiration biopsy every 6 months (35). There were no complications, and adequate samples were obtained in all instances.

IMMUNOHISTOCHEMISTRY AND LABORATORY ANALYSIS

Fine-needle aspiration does not preclude the use of immunohistochemical stains. Both prostate-specific antigen and prostatic acid phosphatase have been used on specimens aspirated from the prostate and lymph nodes and other metastatic sites (36-38).

It is important for one to be aware that, although fine-needle aspiration biopsy is significantly less traumatic to the prostate than is standard histologic core biopsy, it still affects laboratory tests directed toward assessment of prostate cancer. In a study of 14 patients, 8 with adenocarcinoma and 6 with benign prostatic hypertrophy, significant increases in both prostate-specific antigen and prostatic acid phosphatase occurred (39). Thus samples for staging blood tests should be obtained prior to aspiration biopsy.

COMPLICATIONS

A discussion of the relative merits of any procedure should include the incidence of complications. The complication rate of transrectal aspiration is significantly lower than that seen with either perineal or transrectal core biopsy. The complication rate for transrectal core biopsy of the prostate ranges from 17% to 50% with respect to infection, bleeding, and urinary retention (40-43). In comparison to this very high incidence of minor and major complications via the transrectal route, transperineal core biopsy can be expected to result in complications in only 1.1%-6% of the patients (44-46). However, transrectal fine-needle aspiration carries a lower risk of complications than even the perineal biopsy route. In over 3,000

TABLE 7.—Response to estrogen therapy in 44 patients with prostate cancer in a study at University of Umea^a

Cytologic finding	Percent of patients with:								
	Disease regression			Stable disease			Disease progression		
	12 mo	24 mo	36 mo	12 mo	24 mo	36 mo	12 mo	24 mo	36 mo
Regressive changes	50	82	73	45	0	0	5	18	27
No changes	32	32	32	36	27	27	22	41	50

^a See (34).

aspirations, only 12 complications occurred (47,48). These complications included: epididymitis (two), transient hematuria (two), hemospermia (three), and infections (five). This yields an overall complication rate of 0.4%.

CONCLUSIONS

Fine-needle aspiration biopsy of the prostate has been shown to have sensitivity and specificity equal to those of standard core biopsy. No system in use today is individually predictive, but with respect to patient prognosis, cytologic grading of aspiration biopsy samples appears to have a prognostic value similar to that of the histologic grading systems currently in use. The pathologic procedures followed for histologic slides for determination of the origin of a tumor can be performed on aspiration specimens, so accurate interpretation of slides becomes a matter of experience.

Fine-needle aspiration can be performed with less patient discomfort than can core biopsy, and this factor may lead to greater patient acceptance of serial biopsies. Also, the ease of biopsy may lower the clinician's threshold and therefore lead to the detection of a greater percentage of localized lesions. Finally, fine-needle aspiration is associated with a significantly lower complication rate than either transrectal or transperineal core biopsy.

RECOMMENDATIONS TO CONSENSUS PANEL

The following recommendations were made to the National Institutes of Health Consensus Development Panel on the Management of Clinically Localized Prostate Cancer:

- 1) Fine-needle aspiration biopsy should be encouraged as a standard part of the diagnostic armamentarium.
- 2) Fine-needle aspiration biopsy should continue to be performed by urologists because the "learning curve" mandates that core biopsy should be performed concurrently until proficiency is achieved.
- 3) The skills necessary to perform fine-needle aspiration should be acquired by urology residents during their training.
- 4) Pathology residents should develop an expertise in interpretation of prostate aspiration cytology slides.

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Application of Flow Cytometry and Automated Image Analysis to the Study of Prostate Cancer

Mitchell C. Benson^{1,2}

ABSTRACT—Flow cytometry and image analysis are complementary quantitative cytologic techniques that have demonstrated utility in the assessment and analysis of prostate cancer and other urologic and nonurologic tumors. This review is intended to assess the current state of the art and to project future directions and applications of these modalities in the pathologic assessment of prostate cancer. Special attention is directed toward the topics of prostate cancer detection and diagnosis, determination of patient prognosis, and the monitoring of patient response to therapy. We recommend that 1) flow cytometry and image analysis be used to determine pathologic parameters that will help in predicting poor patient prognosis and 2) quantitative cytologic determinations of DNA content be included in clinical trials so that their ultimate role in monitoring patient response to therapy can be determined. This knowledge will allow the development of protocols designed to test the value of earlier institution of multimodal therapy in high-risk populations.—NCI Monogr 7:25–29, 1988.

The application of FCM and automated IA to the assessment and separation of heterogeneous cell populations has added new dimensions to our ability to analyze the nature of tumors. These technologies complement each other and are ideally suited to the analysis of tumors. Conventional microscope-based cytophotometry requires several hours to measure 100 cells, but with FCM and IA we can analyze cells at rates exceeding 100–200/second. In FCM, advances in instrumentation, such as the addition of second and third lasers, plus improved staining techniques now allow for the measurement of many different cell properties on an individual cell. This results in the multiparameter analysis of tumor cell populations. The speed of automated IA has increased because of computerization of the process.

In this presentation, we focus primarily on FCM but also review the application of IA to prostate cancer by discussing the: 1) principles of FCM and cell analysis, 2) cytochemical stains that have been useful in FCM systems, 3) role of quantitative cytology in the diagnosis of prostate cancer, 4) ability of quantitative cytologic systems to portend prognosis, and 5) applicability of these systems to the monitoring of patient response.

FLOW CYTOMETRY

There are currently numerous FCM instruments commercially available. Regardless of which instrument is

used, the basic tenets are the same. These automated cell-analyzing and cell-sorting instruments combine optical and electrical sensing techniques that, with the aid of computer data storage, allow several measurements to be made simultaneously on the same cell. Typical measurements are cell volume, multicolor fluorescence from stains bound to cellular constituents, and light scatter, with which one can assess cell size and intracellular structure.

Proper sample preparation is crucial if meaningful conclusions are to be drawn from the analysis of a specimen. An in-depth discussion of sample preparation can be found in the text by Pretlow and Pretlow (1). For analysis of DNA content only, a technique described by Deitch et al. (2) has proven reproducible and easy to perform. Multiparametric analysis often requires intact, living cells, and we have found (unpublished observation) that adequate numbers of prostatic cells can be obtained from both enzymatic dissociation and mechanical mincing (3). Whenever possible, it is advantageous that one avoid enzymatic digestion because the enzymes can introduce artifacts and alter the affinity of various stains for DNA and cell-surface proteins.

Once a single-cell suspension has been prepared, cell viability should be assessed by trypan blue exclusion. This is necessary for all studies because the use of suspensions with poor viability (<70%) may lead to spurious results due to leakage of cellular components or DNA into the media and analysis of incomplete cells.

The FCM analysis begins by introduction of the cell sample into the flow chamber. Smooth, nonturbulent flow is assured by the introduction of the sample into the center of a faster moving stream of sheath fluid, as described by the Reynolds formulations of fluid flow (4). The proximity of the cells to one another can be controlled by the rate at which sample fluid enters the flow chamber. The speed at which fluid exits the flow chamber is held constant, which allows measurement of multiple parameters at distinct sensing stations along the course of the fluid stream. The distance between the lasers is governed by the physical construction of the flow system, and, because the rate at which a cell is traveling is constant, data can be correlated as having originated from a single source by the time elapsed between readings.

One can accomplish cell sorting by carrying these concepts one step further. A piezoelectric transducer can be activated, and this will cause the fluid stream to vibrate. These vibrations will eventually disrupt the stream and, at a definable point, cause it to break into droplets. Some of these droplets will contain the desired cells. Because the rate at which the stream is traveling is held constant, the distance between the sensors and the deflection plates defines the time at which a droplet containing a desired cell

ABBREVIATIONS: FCM = flow cytometry; IA = image analysis; FLS = forward light scatter; PLS = perpendicular light scatter.

¹ Department of Urology, Columbia-Presbyterian Medical Center, 622 West 168th St., New York, NY 10032.

² I thank Ralph deVere White and John H. Lynch for sharing the results of their studies and Ms. Mary Petway for typing assistance.

will be at the deflection plates. Then by knowing the distance between the sensors and the point at which droplets are forming, one can determine the times at which to activate the deflectors and to place a charge on the desired droplets. For example, a prostate cancer cell has its volume determined at time 0. At times $0 + W$ and $0 + W + X$, various determinations are made, and it is found that this cell type is the one sought. The cell continues to move down the intact sample stream and at time $0 + W + X + Y$, just before it is beginning to be disrupted, the stream is given a positive charge. The stream is then disrupted and the droplet continues to carry this positive charge. The intact stream is then neutralized so that future droplets are not inadvertently deflected. At time $0 + W + X + Y + Z$, the charged droplet containing the desired cell passes through the charged deflector plates and reacts according to the charge placed on the droplet. This reaction allows the cell and others like it to be captured and further analyzed. The process is called cell sorting.

Cells can be sorted directly onto microscope slides for visual identification or sorted into wells containing growth media and subsequently placed in cell cultures. It is our opinion that cell sorting should be a part of any experiment to ensure that one is dealing with true populations and not artifacts.

Most flow cytometers are equipped with laser light sources, the most common of which is the 5-W argon laser because it has substantial power output in both the UV and visual ranges. The main drawback to laser light sources is the expense of the laser. Mercury-arc lamps offer a less expensive alternative and are available on some instruments. For additional information on the techniques of FCM, see (5-8).

CYTOCHEMICAL STAINS

Quantitative cytochemical stains provide a rapid, accurate, and reproducible means of assaying cytologic, biochemical, and functional properties of tumor cells. Measurement of fluorescent dyes that bind to particular cellular constituents has received the most attention in FCM. Additionally, one can combine fluorescent dyes with antibodies and lectins to study cell-surface moieties (9,10).

The measurement of fluorescence has three major advantages in FCM: 1) Fluorescence intensity is directly proportional to the quantity of the dye present and, by inference, to the amount of material being bound. 2) Low concentrations of dye per cell can be detected. 3) Nonfluorescent substrates can be activated to a fluorescent state by cellular enzymes and used to quantitate cellular function (11).

In table 1 is a list of various cellular components and the fluorescent dyes that can help measure each component. This list of the most commonly used dyes is by no means inclusive of all agents in use. The review by Shapiro (12) presents a detailed discussion of the multiple probes in FCM systems. Steinkamp (6) also states some of the uses of multiple dyes in cell assessment.

TABLE 1.—Cellular components and fluorescent dyes used to measure components

Cellular component	Dye
DNA	Hoechst 33342
	Hoechst 33258
	DAPI
	Propidium iodide
	Ethidium bromide
	Acridine orange
	Chromomycin
RNA	Mithramycin
	Pyronine Y
	Acridine orange
Total protein	Oxazine 1
	Fluorescein isothiocyanate
Mitochondria	Sulforhodamine 101
	Rhodamine 123
	Rhodamine B
	Rhodamine 3G
	DiOC

DNA CONTENT

The FCM analysis of prostate cancer has focused predominantly on the quantitation of the DNA content of tumors (13-22).³ The rationale for investigation of the DNA content of tumors of the prostate is based on the results of studies in which researchers used the Feulgen technique of spectrophotometric analysis (23-25). These studies were limited by the small numbers of patients evaluated because of the tedious, time-consuming task of spectrophotometric analysis.

DETECTION AND DIAGNOSIS OF PROSTATE CANCER

To be useful in detection and diagnosis of cancer, a system must have high sensitivity and specificity. The technique must be capable of detecting cancer whenever it is present in the specimen and excluding the diagnosis when cancer is absent. In experienced hands, the sensitivity of histologic and cytologic diagnosis approaches 100%. However, no system can be better than the sample provided for analysis, and in this regard, pathologic examination of both fine-needle aspiration and core biopsy is about 90% accurate (26,27). Approximately 10% of the cancers are not detected on first biopsy, usually because the existing cancer is not present in the biopsy specimen. Thus to be useful in the diagnosis of prostate cancer, the results with FCM or

TABLE 2.—Correlation of incidence of aneuploidy and cytologic grade in 300 patients with prostate cancer^a

Cytologic grade	No. of samples		Percent aneuploid
	Diploid	Aneuploid	
I	79	50	39
II	41	150	78
III	2	69	97

^a See (17).

³ Benson MC, Kaplan SA, Karp F: Submitted for publication.

TABLE 3.—Correlation of incidence of aneuploidy and Gleason score in 190 patients with prostate cancer^a

Gleason score	No. of samples		Percent aneuploid
	Diploid	Aneuploid	
2-4	17	8	32
5-7	28	26	48
8-10	8	21	72

^a See (18,22) and footnote 3.

IA must be equivalent to or better than those with conventional histology and cytology.

Use of FCM in the diagnosis of prostate cancer relies on the presence of an abnormal DNA histogram. Unfortunately, abnormalities (frank aneuploidy or >10%–15% growth fraction) occur in normal samples, and not all prostate cancers demonstrate these changes. A new technique with the DNA index of nonmalignant prostatic tissue as the reference standard has shown promise as a means to enhance sensitivity.³ In most studies, lymphocytes are used as a diploid reference standard. The DNA index is then defined as the quotient of sample DNA/lymphocyte DNA. An index of 1.00 has traditionally been considered normal. Due to variation in either available staining sites on the chromosomes or fluorochrome uptake into the nucleus, other normal tissues may have a slightly higher or lower index. The new technique uses the DNA index of normal prostate (1.04) as the reference standard, and a patient-specific index is determined by the patient's prostate DNA/patient's WBC DNA. In a series of 12 patients, this new index system has shown great sensitivity in detection (100%), but specificity has not been addressed.

Tables 2 and 3 present the incidence of aneuploidy as a function of cytologic grade and Gleason score. The tables demonstrate that with increasing tumor grade or Gleason score, the incidence of aneuploidy increases. The lack of sensitivity of standard DNA histogram analysis in detecting prostate cancer is evidenced by the fact that 2 of 71 specimens with grade III cytology and 8 of 29 specimens with Gleason scores 8–10 demonstrated seemingly normal diploid DNA patterns (17,18,22).

Systems that rely solely on DNA determination are not specific and sensitive enough to be used in the detection and diagnosis of prostate cancer. Sensitivity may have been improved by the incorporation of tissue-specific controls, but further study is necessary.

QUANTITATIVE CYTOLOGY IN DETERMINATION OF PROGNOSIS

Histologic aggressiveness not discernible by standard histopathology has been predicted successfully by FCM and IA (18,20–22,24,25,27,28). In a study on fine-needle aspiration biopsy specimens, DNA determinations were made according to a cytophotometric technique. Because this was a manually performed analysis, the number of cells assessed per patient was less than 100. Survival was correlated with percent hyperdiploid cells (25). The authors selected 43 patients with similar grade (I–III) and stage (B and C) characteristics. Twenty-one of the patients survived more than 5 years; 22 died within 3 years. Fourteen of the 21

TABLE 4.—Correlation of DNA ploidy, Gleason score, and tumor stage with percent survival at 5 yr in 59 patients with prostate cancer^a

Pathology	Percent survival	
	Aneuploid	Diploid
Gleason score		
2-4	67	93
5-7	33	71
8-10	29	50
Stage		
A + B	67	90
C + D	7	29

^a See (22).

patients demonstrated predominantly diploid tumors, compared with only 4 of the 22.

Three studies have been conducted in which patient survival was correlated with DNA content as determined from analysis of paraffin-embedded tissue (21,22,28). The study by Lundberg et al. (21) correlated histopathologic grade and DNA ploidy with survival in 50 patients. No correlation between ploidy and grade was found, but a statistically significant relationship between survival and ploidy was demonstrated. Fordham et al. (28) analyzed 72 patients and found that when ploidy was correlated with Gleason score, significant prognostication could be made. They found that for Gleason scores of 7–10, all the 19 patients with aneuploid tumors died within 3 years, compared with only 6 of 10 with diploid tumors. For Gleason scores of 2–6, they found that 2 of 6 patients with aneuploid tumors died within 3 years, but only 3 of 17 with diploid tumors died. Lastly, in a study of 54 patients by Dejtter et al. (22), DNA ploidy, Gleason score, and tumor stage were correlated with percent survival at 5 years (table 4). These data demonstrate that within stage and grade categories the incidence of aneuploidy portends prognosis.

In comparison to these studies, which demonstrate that the incidence of aneuploidy correlates inversely with survival, deVere White and Deitch (unpublished observations), using fresh and paraffin-embedded tissue, determined that patients with aneuploidy responded better to hormonal therapy and, in those with stage D disease, it had a direct correlation with prolonged survival (table 5). It is not at first apparent why the results in this series differed from those in other series. As suggested by the authors, diploid tumors may be less hormone responsive because of lower growth fractions, as determined by pretreatment ploidy. Also possible is that this represents a sampling phenomenon. However, these data underscore the necessity of our stratifying patients in research protocols by DNA ploidy.

TABLE 5.—Correlation of DNA ploidy and Gleason score with percent survival at 30 mo in 77 patients with prostate cancer^a

Gleason score	Percent survival		
	Total	Aneuploid	Diploid
5-7	73	100	50
8-10	50	75	20
Total	64	82	36

^a deVere White RA, Deitch AP: Unpublished observations.

There is a 61% reported incidence of aneuploidy when any DNA pattern other than diploid is considered to be aneuploid. This value is obtained from the pooling of data from seven published series comprising 331 patients (16,18,29).

The studies cited here correlated prognosis and disease extent by DNA content. Similar studies have been performed with light scatter measurements.

LIGHT SCATTER

As cells pass through the laser beams of a flow cytometer, incident light reflects, diffracts, and refracts from the surface and internal structures of the cell. The combination of these phenomena is known as light scatter. Although light scatter could be measured at any angle from the incident light source, the commercially available flow cytometers are designed to measure light scatter in the forward and perpendicular directions. In FCM systems, FLS has been shown to correspond directly to the size of the object being studied (30). Thus the larger the cell, the more intense are the FLS signals.

The PLS intensity is also related to cell size, but more importantly, it measures internal cellular structure (30-32). Because the largest internal structure in prostate cancer cells is the nucleus, PLS predominantly measures nuclear surface area. Nuclear surface area is a function of size and shape, and by comparing PLS to nuclear IA by manual digitization, one can see that PLS intensity is directly proportional to nuclear size and shape (32). Although PLS and FLS have not been widely used in the study of human prostate cancer, evidence in animal systems suggests that the combination of these parameters can be used in quantitative grading of tumors on the basis of cell size and nuclear shape (33).

Preliminary studies in humans undergoing radical retropubic prostatectomy have demonstrated that the combination of FLS and PLS can help predict pathologic stage (3). Some have used this technique to assess not only mean light scatter values but also intratumor variation. It is believed that the variation in signals is an estimate of tumor cell heterogeneity and that tumor heterogeneity is related to tumor aggressiveness. The authors reported on only 7 patients, but a grading index based on FLS and PLS values correlated well with pathologic stage in the incidence of seminal vesicle invasion and capsular penetration. This series will have to be expanded and confirmed by others before its true usefulness will be known.

QUANTITATIVE CYTOLOGY TO MONITOR PATIENT RESPONSE

Because aneuploidy is usually accepted as being associated with more aggressive tumors, it is logical for one to assume that a patient responding to therapy should demonstrate a diminution in the hyperdiploid population of the tumor (34). Such a pilot FCM study was performed by Kjaer et al. (35) in patients treated with estrogenic compounds. Six of the 8 patients demonstrated aneuploidy and 2 had diploid tumors. Four of the 6 patients with aneuploid tumors responded to therapy, and at a biopsy 2-3 months after the initiation of therapy, this was evidenced by reduc-

tion or disappearance of the aneuploid population. The 2 patients with diploid tumors also demonstrated good hormonal response and their histograms remained unchanged.

Using cytophotometric analysis, Leistenschneider and Nagel (36) examined 15 patients with cytologic grade III tumors and found that response to estramustine could be monitored by the disappearance of aneuploidy and the development of a diploid sample. Additionally, they suggested that relapse following radiation therapy could be similarly monitored.

A similar conclusion was reached by Bouffieux (37), who also used a cytophotometric technique. He concluded that the persistence or reappearance of aneuploidy is evidence of therapeutic escape and, even in the absence of clinical disease progression, should be accompanied with a change in treatment.

CONCLUSIONS

Quantitative cytologic analysis by FCM and automated IA have been applied successfully to the analysis of prostate cancer. To date, it appears that use of these techniques does not result in accurate diagnosis, and physicians should not rely on them as a means to detect prostate cancer. Although newer techniques may have adequate sensitivity in the screening of known cancer populations, specificity remains to be determined.

Quantitative cytology does appear to be useful in portending patient prognosis. These techniques have predictive value independent of and in some cases beyond that of cytologic analysis or Gleason score and tumor stage. The DNA analysis has also been shown to be a sensitive monitor of patient response. The persistence or re-emergence of aneuploidy following endocrine or radiation therapy appears to be an early harbinger of disease progression.

RECOMMENDATIONS TO CONSENSUS PANEL

The following recommendations were made to the National Institutes of Health Consensus Development Panel on the Management of Clinically Localized Prostate Cancer:

- 1) Quantitative cytologic determination of DNA content should be included in clinical protocols to monitor patient response.
- 2) Because these techniques seem to have the potential to identify populations with a particularly poor prognosis, protocols should be developed that test the use of early multimodal therapy in high-risk populations.

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Noninvasive Imaging for Staging of Prostate Cancer: Magnetic Resonance Imaging, Computed Tomography, and Ultrasound

Hedvig Hricak¹

ABSTRACT—The diagnosis of prostate carcinoma by imaging is still fraught with problems, even with the advent of highly sophisticated techniques. Despite enthusiastic preliminary reports, no one imaging method reliably screens for this condition. The staging of prostate carcinoma is feasible, but the best imaging method remains a subject of debate. The transabdominal sonographic approach lacks the resolution required for detailed intraglandular anatomic delineation. The transrectal sonographic approach excels in guiding needle biopsy and in evaluating transcapsular and seminal vesicle extension of known tumors. Computed tomography lags behind other tomographic imaging modalities in its accuracy for local tumor staging, but it is excellent, although nonspecific, in the detection of lymph node enlargement. Magnetic resonance detects abnormalities in the prostate in a high percentage of cases but is nonspecific. However, it can stage prostate carcinoma and detect lymphadenopathy reliably.—NCI Monogr 7:31–35, 1988.

The diagnostic armamentarium for the detection and staging of prostate carcinoma is extensive, yet numerous problems persist. Despite many enthusiastic reports, no diagnostic imaging modality is specific for the detection of prostate cancer. The decision on which is the best, most accurate, staging modality remains controversial.

ULTRASONOGRAPHY

The prostate gland can be examined sonographically through the transabdominal, transrectal, and transurethral approaches. The suprapubic abdominal approach is simple and does not require a dedicated, specialized transducer (1). Due to the depth of the prostate gland, the transabdominal approach is hampered by the need for a low-frequency (3.5 MHz) transducer (fig. 1), which limits the spatial resolution and thus the detection and evaluation of intraprostatic disease (2).

The transrectal and transurethral approaches provide a much better assessment of the prostatic parenchyma. As the distance between the rectal transducer and the prostate is short, high-frequency transducers (5–10 MHz) can be used. This markedly improves spatial resolution and allows better assessment of the anatomy and pathology of the prostate. Transrectal sonography in sagittal projection is optimal for evaluation of the craniocaudal margins of the gland. In the transrectal transverse scan, the relationships among the prostate, prostatic capsule, and levator ani are well displayed. Two planes of imaging are essential for the complete examination of the prostate by ultrasound (3).

Many reports have enthusiastically addressed the use of transrectal ultrasound for screening (4). However, in actuality, its use for screening lacks sensitivity (defined as the number of true-positive cases divided by the sum of the true-positive and false-negative results). When compared with findings at pathologic examination (fig. 2), the reported sensitivity has ranged from 62% (2) to 65% (5). Furthermore, sonographic tissue characterization lacks specificity (defined as the number of true-negative cases divided by the sum of the true-negative and false-positive results). Biopsy remains essential (1–6). However, if an abnormality within the prostate is demonstrated on the sonogram, ultrasound is an excellent modality to guide needle biopsy.

In the staging of prostate carcinoma, i.e., in evaluation of transcapsular and seminal vesicle extension, transrectal ultrasound is advocated as having the greatest accuracy (defined as the sum of the true-positive and true-negative cases divided by the total number of patients). In the evaluation of transcapsular tumor extension, the accuracy of this modality ranges from 64% to 90%, the specificity from 78% to 94%, and the sensitivity from 59% to 86% (6,7). The demonstration of seminal vesicle involvement is more difficult, resulting in an accuracy range of 77% to 85% and a low sensitivity ranging from 29% to 33% (6,7). The accuracy of ultrasound for detection of transcapsular tumor extension is significantly higher than that of computed tomography (7). When tumor extension to the bladder neck, rectum, or pelvic lymph nodes needs to be evaluated, ultrasound is limited.

The use of transrectal ultrasound for the local staging of the prostate carcinoma (assessment of disease confined to the prostate) needs further evaluation with correlation between histopathology and ultrasound findings. However, it should be emphasized that the small field of view limits complete evaluation of the pelvis, and ultrasound is at present not acceptable for lymph node evaluation.

COMPUTED TOMOGRAPHY

Computed tomography can display abnormalities in contour of the gland, but it does not have sufficient soft-tissue contrast to provide information about disease within the gland. Staging by computed tomography has been shown to have significant limitations (8–10). Carcinoma generally has the same attenuation value as the remainder of the prostatic parenchyma and will not be identifiable unless it extends outside the gland. The diagnosis of stages A and B (carcinoma confined to the gland) is derived by exclusion (11), when the lesion fails to produce changes in the gland contour. The role of computed tomography in the evaluation of patients with prostate neoplasms is not to confirm

¹ Department of Radiology, University of California, San Francisco, Box 0628, San Francisco, CA 94143-0628.

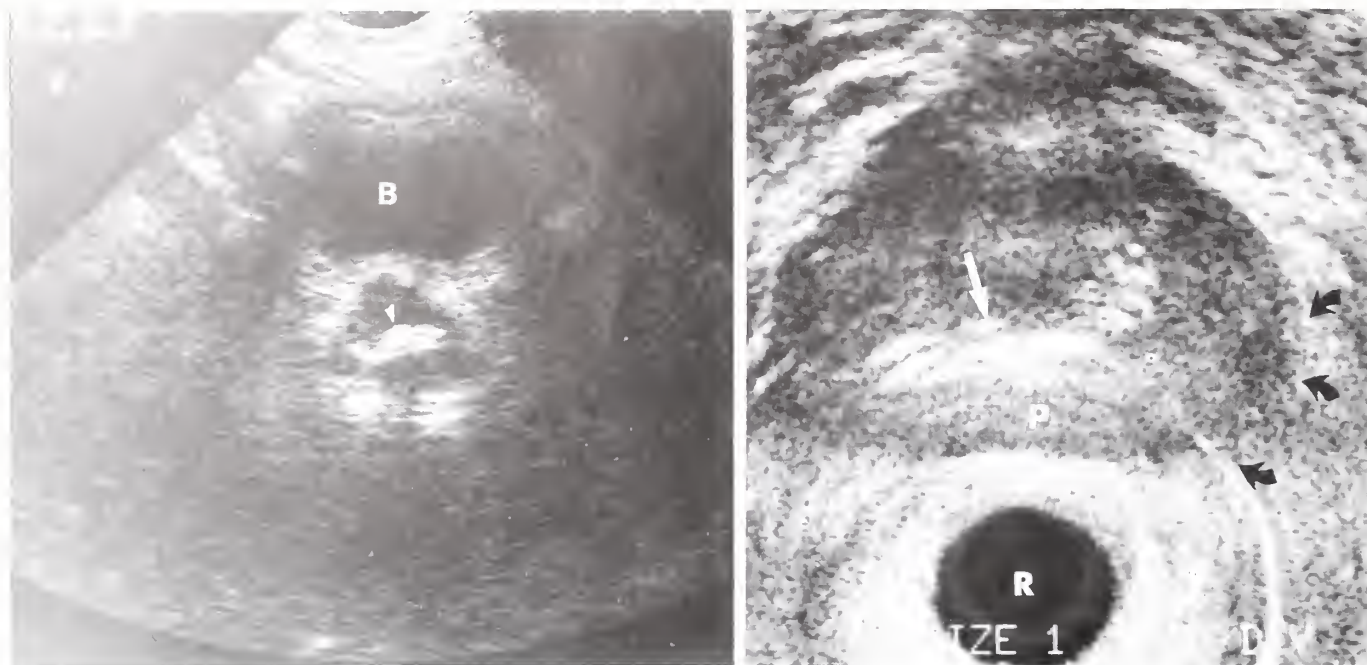


FIGURE 1.—Stage B2 prostate carcinoma. *Left:* Transabdominal ultrasound 3.5-MHz transducer. *Right:* Transrectal ultrasound 7.5 MHz. Calcifications (long arrow) are seen within the prostate. On a transrectal scan, calcifications are at the junction of the central gland and peripheral zone (P). Note bulging of the left lateral contour of the gland (arrows), and, although the margin appears indistinct, no periprostatic tumor extension was seen at surgery. Spatial resolution of the transrectal scan is superior to the transabdominal.

the presence of disease but to delineate the extent of tumor spread and identify local pelvic and abdominal adenopathy. Its sensitivity in the detection of transcapsular tumor invasion is 25%, specificity 89%, and accuracy 60% (7).

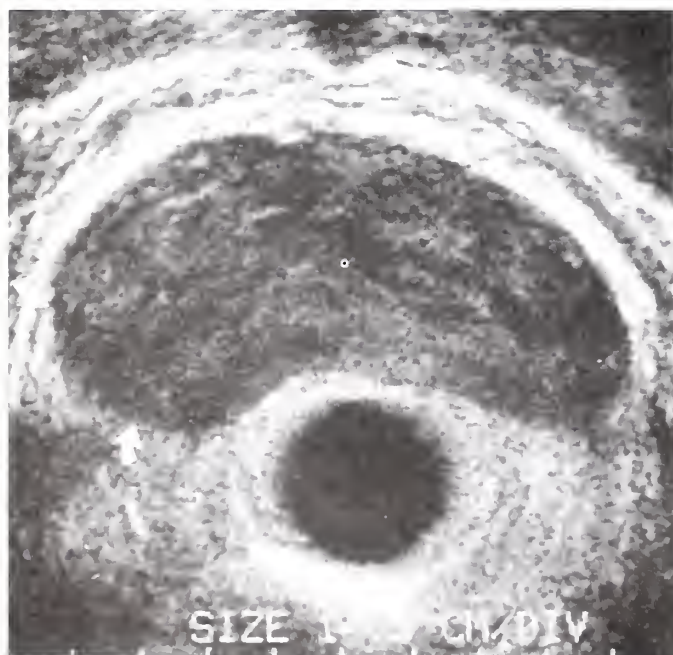


FIGURE 2.—Stage B2 prostate carcinoma. Transrectal ultrasound. Gland is enlarged, but the echogenicity throughout the peripheral zone is homogeneous. At surgery, a B2 lesion was present in the right side (arrow) of the gland.

These findings are significantly lower than those of either transrectal ultrasound (7) or magnetic resonance imaging (12). The sensitivity of computed tomography in detecting seminal vesicle involvement was 36%, specificity 96%, and accuracy 76% (7), similar to those of transrectal ultrasound (7). As with ultrasound, computed tomography cannot accurately identify extension into the bladder base, as this is a transverse interface parallel to the transverse imaging plane of the tomography. The potential for understaging and overstaging is thus significant. Obliteration of the seminal vesicle angle with enlargement of the seminal vesicle is suggestive of tumor extension, but the specificity of this finding is questionable. The evaluation of lymph node involvement by computed tomography is also limited. The reported sensitivity ranges from 50% to 75%, the specificity from 86% to 100%, and the accuracy from 83% to 92% (8-10). Morphologic criteria alone (size) determine lymph node involvement; a decrease in the size threshold will give fewer false-negative results, but the false-positive rate will increase (fig. 3). Normal-sized nodes often are not detected in the pelvis. Patients with false-positive results usually have fibrotic, hyaline, or histiocytic changes in enlarged nodes. Lymphadenectomy or fine-needle aspiration is required for accurate diagnosis, with the risk of increased morbidity.

MAGNETIC RESONANCE IMAGING

Initial results of the evaluation of prostatic disease by magnetic resonance imaging were promising, but as more experience has been gained, reports have conflicted (12-16). Excellent tissue contrast by magnetic resonance imaging allows depiction of intraprostatic anatomy, differ-

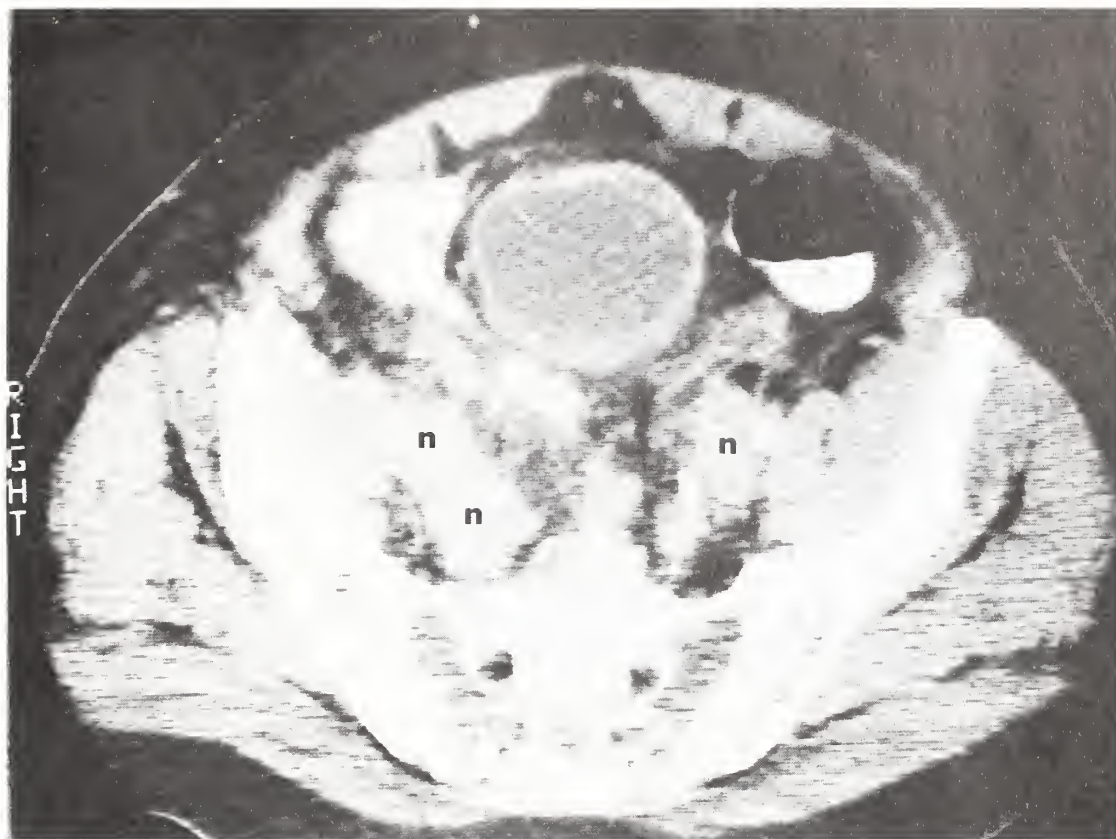


FIGURE 3.—Stage D1 prostate carcinoma. Lymph nodes are markedly enlarged (n) bilaterally.

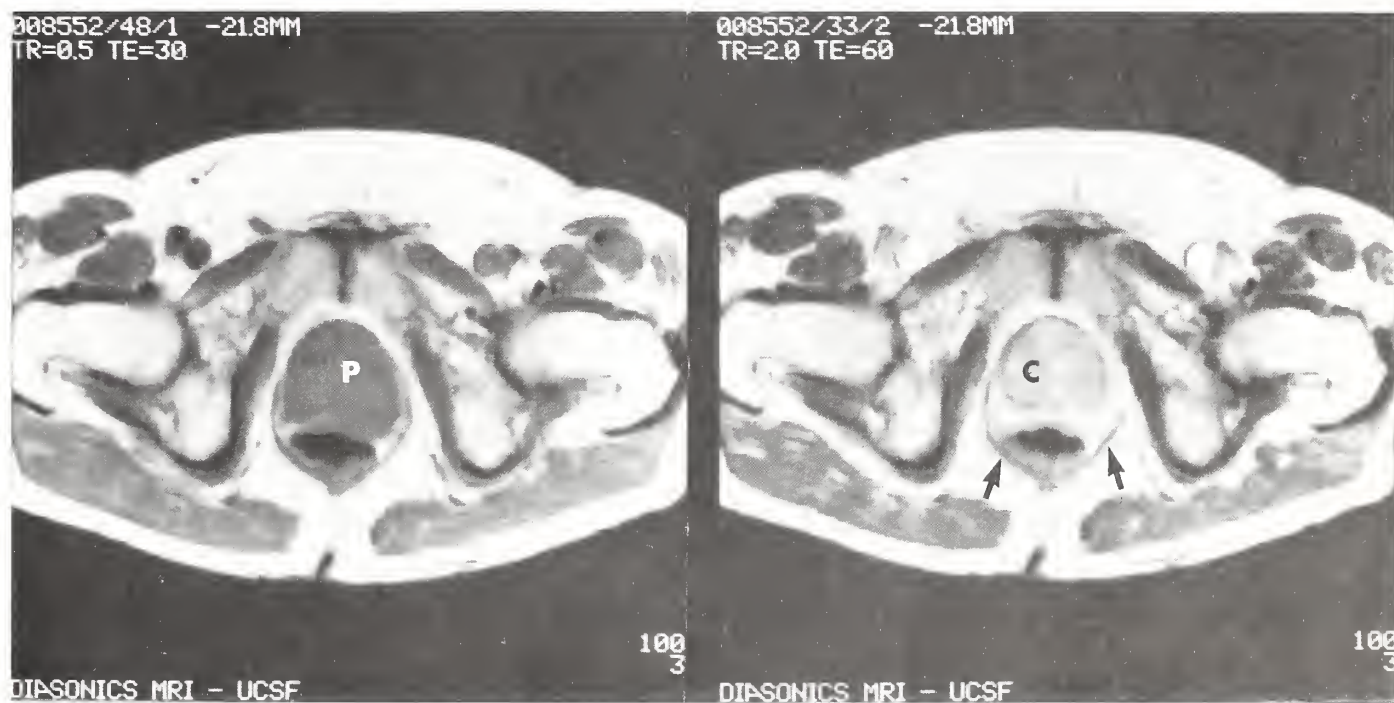


FIGURE 4.—Stage B2 prostate carcinoma. *Left*: T1-weighted image (spin echo) SE 500/30. *Right*: T2-weighted image SE 2,000/60. Prostate (P) is enlarged. On T1-weighted image, contrast is excellent between prostate parenchyma and surrounding periprostatic tissue. No tumor spread outside the prostate is identified. On T2-weighted image, central gland of the prostate (C) is of low signal intensity and can be differentiated from higher signal intensity peripheral zone. Levator ani muscles (arrows) are clearly visualized and are of normal signal intensity.

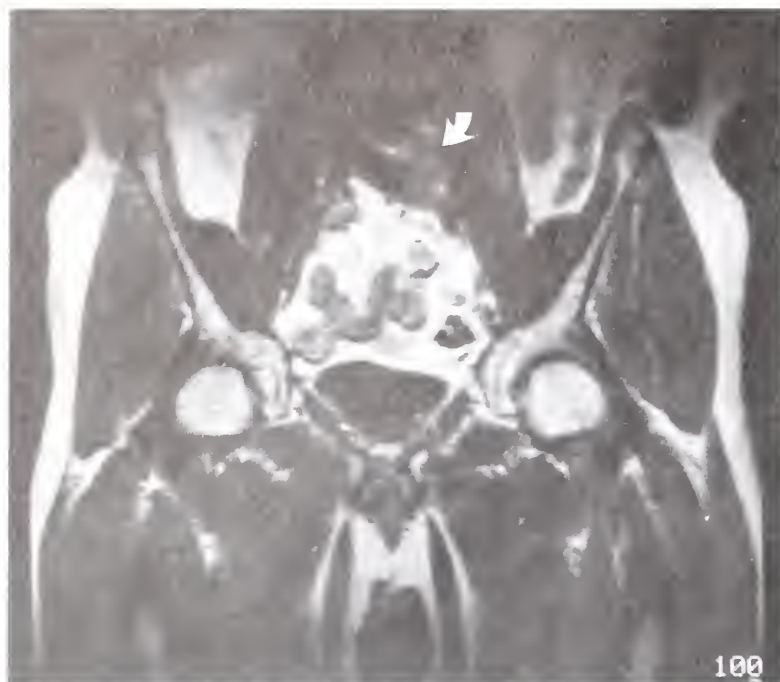


FIGURE 5.—Stage D1 prostate carcinoma. Bilaterally enlarged lymph nodes (*curved arrow*) are identified. However, it is only the size of the node (1 to 1.5 cm in length) that can be detected on magnetic resonance imaging, which cannot distinguish malignant from hyperplastic nodes; biopsy is essential.

entiating the peripheral, central, and transition zones (17). Disease confined to the gland can be detected by magnetic resonance imaging; however, there is overlap between the appearance of benign and malignant conditions when this modality is used (14). Thus findings are not specific, and magnetic resonance is not suitable as a screening modality (12). Once carcinoma is histologically documented, it is valuable for staging the disease, with reported accuracy between 83% and 89%, sensitivity between 75% and 87%, and specificity from 88% to 90% (12-16). Results from magnetic resonance imaging are significantly higher than those of computed tomography or clinical examination. However, an extensive imaging protocol is needed for accurate imaging results (fig. 4). This must include combinations of various imaging parameters and images obtained in two orthogonal planes. The transverse plane is valuable for assessment of the relationships among the prostate, prostatic capsule, and levator ani as well as for the detection of lymphadenopathy. The sagittal plane is preferred in patients who have undergone transurethral resection of the prostate or in whom bladder or rectal involvement is suspected. Coronal images offer an additional view of the periprostatic fossa, levator ani, and possible lymph node metastasis (fig. 5). In detecting lymph node metastases, we find magnetic resonance imaging results are similar to those of computed tomography, and lymph node biopsy for histologic diagnosis is still essential.

SUMMARY

At present, no imaging modality can be relied upon as a diagnostic method for prostate carcinoma. Perhaps the combination of physical examination, transrectal ultrasound, and ultrasound-guided biopsy will be the best approach for prostate cancer detection. For staging of prostate

carcinoma, a uniform staging system is crucial for patient management. The use of computed tomography for local staging of the disease has not been widely accepted because the results are similar to those of clinical examination. However, the accuracy rates of both transrectal ultrasound and magnetic resonance imaging for local staging of the disease are significantly higher than those of either computed tomography or clinical studies. A combination of transrectal ultrasound and magnetic resonance imaging appears to yield the best results, but further studies are necessary for confirmation. The sensitivity of imaging needs to be explored further, and a larger series should be studied for an analysis of combined staging methods by ultrasound and magnetic resonance imaging that would address not only the accuracy but also the impact of staging on the therapeutic approach.

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Lymphography in Clinically Localized Prostate Cancer

Ronald A. Castellino¹

ABSTRACT—Lymphography demonstrates the size, position, and internal architecture of the external iliac, common iliac, para-aortic, and paracaval lymph nodes. Importantly, the “surgical obturator” nodes are also routinely opacified because they are part of the external iliac chain. Analysis of the internal architecture permits detection of metastases in nodes of normal size, an advantage over cross-sectional imaging techniques. In a prospective study of 89 unselected, previously untreated patients with carcinoma limited to the prostate or periprostatic bed, lymphography was compared with histology of lymph nodes removed at surgical staging. The sensitivity was 53% (17 of 32), specificity 93% (53 of 57), accuracy 79% (70 of 89), and positive and negative predictive values were 81% (17 of 21) and 78% (53 of 68), respectively.—NCI Monogr 7:37–39, 1988.

Patients with newly diagnosed carcinoma of the prostate undergo a rigorous evaluation by physicians to determine the anatomic extent of disease because this has significant implications in patient management and prognosis. In certain patients, assessment of the regional (pelvic) lymph nodes is important as most urologic surgeons will not perform radical prostatectomy in this patient population; rather, the patient will be recommended for alternative therapy, such as external-beam radiotherapy. In this subgroup of patients, clearly the best assessment of regional lymph nodes is by surgical removal and histologic evaluation. However, this commits the patient to a surgical procedure that could be obviated, if an acceptable noninvasive evaluation of the lymph nodes could be performed.

Lymphography permits accurate radiographic display of the size, position, and internal architecture of the external iliac, common iliac, para-aortic, and paracaval lymph nodes to the level of the renal vascular pedicle. Although the internal iliac (hypogastric) lymph nodes are not routinely or completely opacified, importantly the so-called “surgical obturator” nodes are routinely opacified, inasmuch as they are part of the medial external iliac lymph node chain (1,2). Careful analysis of the internal architecture of each lymph node permits detection of lymph node abnormalities compatible with metastases within nodes that are still normal in size. This is an advantage over current cross-sectional imaging techniques (computed tomography, ultrasound, and magnetic resonance imaging),

which rely upon nodal enlargement to detect adenopathy. False-positive lymphographic diagnoses are relatively uncommon and are mainly the result of defects caused by nonspecific changes, i.e., fat, fibrosis, and hyperplasia. False-negative lymphographic interpretations are relatively common, due primarily to small metastatic deposits that produce minimal structural alterations within the lymph nodes or to metastases to the deeper pelvic nodes that are not opacified.

Lymphography is a minimally invasive procedure that is performed on an outpatient basis. Small (1–2 cm) superficial incisions over the dorsum of both feet are made to isolate the small lymphatic channels in the subcutaneous tissues, followed by their cannulation. The procedure requires some technical skill and experience to perform, factors which have discouraged many radiologists from developing expertise in either the performance or subsequent interpretation of these studies.

An accurate assessment of sensitivity, specificity, overall accuracy,² and positive and negative predictive values of lymphography, and particularly of other imaging techniques, is hampered by the paucity of carefully performed prospective clinical studies. Reports based upon selected patients, small numbers of patients, patients with varying stages of disease or at varying times during the course of their illnesses, and lack of pathologic correlation with the imaging study interpretation provide information that can be misleading and provide little confidence for subsequent decision-making. However, there are several relatively large series of patients with clinically localized carcinoma of the prostate, who underwent lymphography followed by lymph node biopsies, which provide some insights into accuracy for this technique in this patient population.

The Stanford experience [(3); Castellino RA: Unpublished observation] encompasses 89 unselected, previously untreated patients with disease limited to the prostate (clinical stage A or B) or periprostatic bed (clinical stage C), without evidence of metastases based upon clinical assessment, laboratory studies, and skeletal radioisotopic and/or radiographic surveys. The lymphograms were interpreted as positive or negative for metastatic disease; no equivocal diagnostic category was utilized. The cannulation was successful bilaterally in all but 2 patients. The 2 unilateral studies are included in the analysis even though the lack of contralateral opacification compromised diagnostic effectiveness. Following lymphographic interpretation, the nodes of greatest concern were indicated on the radiographs. The patients underwent multiple lymph node biopsies at various anatomic sites to permit subsequent radiographic/histologic correlations. Assessment of postoperative abdominal films confirmed if the nodes of concern were adequately sam-

¹ Department of Diagnostic Radiology and Nuclear Medicine, Room S078, Stanford University Medical Center, Stanford, CA 94305.

² Sensitivity is the percentage of patients with histologically positive nodes whose lymphograms were correctly interpreted as positive; specificity is the percentage of patients with histologically normal nodes whose lymphograms were correctly interpreted as negative; overall accuracy is the percentage of patients whose lymphograms were correctly interpreted as positive or negative.

TABLE 1.—Lymph node histology of surgical specimens from unselected, previously untreated patients with prostate cancer: Stanford experience

Clinical stage	No. of patients	Histologically positive nodes			
		Pelvic		Lumbar	
		No.	Percent	No./total No. of patients	Percent
A	2	0			
B	47	9	19	2/9	22
C	40	23	58	11/23	48
Total	89	32	36	13/32	41

pled. (In 2 additional patients, the lymphographically positive nodes were not removed, and their results are not included in this analysis.)

One or more excised pelvic lymph nodes were histologically positive in 19% (9 of 47) of clinical stage B and 58% (23 of 40) of clinical stage C patients. Histologically positive para-aortic or paracaval lymph nodes were noted in 22% (2 of 9) and 48% (11 of 23) of this group of patients, respectively (table 1). In no instance was there retroperitoneal, without concomitant pelvic, lymph node involvement.

Lymphographic-histologic correlation (table 2) for the whole group of patients revealed a sensitivity of 53%, specificity of 93%, and accuracy of 79%, and predictive values of positive and negative tests in 81% and 78%, respectively. A breakdown of these accuracy data for the patients with clinical stages B and C disease is provided in table 3.

A similar study was performed by the Uro-Oncology Research Group (4). This was a multi-institutional study and all lymphograms were interpreted by 1 referee radiologist. Their data, accumulated from 149 patients undergoing lymphography followed by surgical lymph node sampling, revealed a sensitivity of 56%, specificity of 95%, and accuracy of 81%, with predictive values of positive and negative tests in 86% and 79%, respectively (table 4). These results are quite similar to the Stanford experience.

Currently, lymphography is the most accurate diagnostic imaging study in the assessment of the external and common iliac nodes and para-aortic and paracaval nodes to the level of L1-2. Although increasingly accurate in patients with advanced disease (in which both the incidence and the bulk of lymph node involvement are greater), this technique has significant false-negative diagnoses when patients

with apparently localized prostate carcinoma are evaluated. A negative lymphographic interpretation is therefore unreliable, as are other negative clinical, laboratory, and diagnostic imaging evaluations, all of which are insensitive to relatively minimal amounts of disease. On the other hand, a positive lymphographic interpretation does possess a relatively high predictive value, which, not surprisingly, is greater in clinical stage C, as compared with clinical stage B, patients. Thus a positive lymphographic diagnosis merits strong consideration for lymph node metastases. In those instances in which the lymphographic findings are suspicious but not compelling, or in which the clinical presentation is discordant with the lymphographic findings, further evaluation can be provided with fluoroscopically guided percutaneous needle aspiration. This technique is also performed on an outpatient basis and is associated with minimal morbidity and rare complications. A positive lymph node aspiration provides meaningful information; however, a negative node aspiration does not exclude the presence of metastases, and this procedure can be repeated, as indicated.

Although experience with magnetic resonance imaging is still being accumulated, this technique should possess similar diagnostic accuracy as does computed tomography, and perhaps may be better due to the confidence with which vessels can be distinguished from lymph nodes. Although both techniques require enlarged lymph nodes for a diagnosis of adenopathy, they are noninvasive and require little technical skill for performance of the procedures. Furthermore, many radiologists are very skilled in the performance and interpretation of cross-sectional imaging examinations. Evaluation of the prostate itself, determination of the local extension of tumor, and assessment of other organ systems are additional benefits of computed tomography and magnetic resonance imaging studies.

The following is proposed as a possible strategy in assessment of the regional lymph nodes in patients with apparently clinically localized prostate carcinoma.

- 1) First, and most important, only those patients need to be evaluated in whom the status of the lymph nodes will have impact upon their management.
- 2) Clinical evaluation and histologic assessment of the biopsy material will frequently determine a subgroup of patients in whom the likelihood of lymph node metastases is very small, or in whom lymph node metastases are likely to be relatively small in size, e.g., those with early stage disease and/or low Gleason scores. In these patients, lymph node imag-

TABLE 2.—Lymphography and pathology results: Stanford experience

Clinical stage	No. of patients	No. of patients with:			
		Positive lymphography and lymph node biopsy	Negative lymphography and positive lymph node biopsy	Negative lymphography and lymph node biopsy	Positive lymphography and negative lymph node biopsy
A	2			2	
B	47	2	7	35	3
C	40	15	8	16	1
Total	89	17	15	53	4

TABLE 3.—Lymphographic-pathologic correlations: Stanford experience

Interpretation of results	Clinical stage					
	Total		B		C	
	Percent		Percent		Percent	
Sensitivity	53	17/32	22	2/9	62	15/23
Specificity	93	53/57	92	35/38	94	16/17
Accuracy	79	70/89	79	37/47	78	31/40
Positive predictive value	81	17/21	40	2/5	94	15/16
Negative predictive value	78	53/68	83	35/42	67	16/24

ing studies will have a low yield indeed and could well be dismissed.

- 3) In patients with a likelihood of lymph node metastases, arguments could be supported that a cross-sectional imaging study be performed first that may demonstrate obvious lymph node or distant metastases. This would obviate the need to perform lymphography.
- 4) Lymphography would then be reserved for those patients for whom information about the lymph nodes is important for management, in whom enlarged lymphadenopathy has been excluded by computed tomographic and magnetic resonance scanning, and in whom metastases within normal size or only modestly enlarged lymph nodes may be detected by lymphographic examination.

a) A positive or suspicious study can be confirmed by percutaneous needle aspiration, if such reassurance is needed. This will obviate patients being denied a potentially curable procedure on the basis of a false-positive diagnostic imaging study.

b) A negative study does not exclude metastases. Further evaluation, such as by surgical lymph node sampling, will need to be considered, depending upon the importance of such information in patient management.

- 5) Should local expertise in performing and interpreting lymphograms not be available, this evaluation could be performed in regional centers by specialists with experience.

TABLE 4.—Results of 149 patients undergoing lymphography followed by surgical lymph node sampling^a

Interpretation of results	Percent	
Sensitivity	56	30/54
Specificity	95	90/95
Accuracy	81	120/149
Positive predictive value	86	30/35
Negative predictive value	79	90/114

^a Patients were in the Uro-Oncology Research Group studies. See (4).

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Value of and Indications for Pelvic Lymph Node Dissection in the Staging of Prostate Cancer

Richard G. Middleton¹

ABSTRACT—Pelvic lymphadenectomy is valuable as a staging procedure prior to radical prostatectomy in patients with clinical stages A2, B1 (except low-grade lesions), and B2 prostate cancer who seem to be good candidates for an attempt at curative surgery. Survival rates are promising in patients with negative pelvic lymph nodes and local tumors who undergo radical prostatectomy. In the presence of positive nodes, there is little reason to proceed with radical prostatectomy. Noninvasive alternatives to pelvic node dissection are appealing, but lymphangiography, ultrasound, computed tomography scanning, and magnetic resonance imaging are all less reliable than pelvic lymphadenectomy. Some morbidity is associated with surgical staging, and it is important that this be minimized. Pelvic lymph node dissection can play a role in treatment planning for patients who will be given external-beam radiation therapy. However, the role depends on the physician's treatment philosophy. In a recently reported series of patients receiving radiation therapy for localized prostate carcinoma, prior surgical staging by pelvic lymphadenectomy is uncommonly performed.—NCI Monogr 7:41-43, 1988.

There is little evidence that pelvic lymphadenectomy is beneficial therapeutically in prostate cancer. The value of pelvic lymph node dissection is as an accurate staging procedure when the need to know precisely the state of the pelvic lymph nodes is vital and when significant clinical decisions depend on accurate information. Pelvic lymphadenectomy for staging is generally indicated when prostate cancer seems to be localized clinically and when the patient seems to be a good candidate for therapy with curative intent, i.e., radical prostatectomy or radiation therapy. When metastasis to the pelvic lymph nodes has occurred, the patient already has systemic disease and is unlikely to benefit from aggressive attempts to eradicate the primary prostate cancer. Although some urologic surgeons proceed with radical prostatectomy in the presence of positive pelvic lymph nodes, most, including myself, recognize that the tumor at this stage is almost inevitably progressive, and we think that radical prostatectomy is not appropriate in the presence of pelvic nodal metastasis. Other palliative measures, either early or delayed, are more reasonable.

The prognosis for a patient with pelvic lymph node metastasis is ominous. About 75% of the patients with positive pelvic nodes develop bony metastasis within 5 years, and about 40% die of prostate cancer within 5 years of detection of nodal metastasis (1). Once nodal metastasis has occurred, the rate of tumor progression is related to the volume of nodal disease and to the tumor grade; local or regional therapy has little effect on the progression (1,2).

Radical prostatectomy may decrease the incidence of local problems in the pelvis, but the benefits are slight.

On the other hand, when the tumor is clinically localized to the prostate and lymph nodes are negative, as determined by lymphadenectomy, the results of radical prostatectomy are encouraging. From the University of Utah, we have reported (3) on 136 patients with clinical stages A2, B1, and B2 prostate cancer and proven negative pelvic nodes who have had radical prostatectomy and follow-up for 5 years after surgery (table 1). At 5 years following radical prostatectomy, 128 patients (94%) were alive and 118 (87%) were alive and well without evidence of tumor recurrence. The outcome for those with stages A2 and B1 disease and negative pelvic nodes was particularly good, i.e., 91% in each category were alive and free of tumor recurrence at 5 years. Patients with B2 tumors and negative pelvic nodes fared less well, but 81% were alive and free of tumor at 5 years. In our experience, patients with prostatic capsular invasion (surgical stage C disease) did as well at 5 years as those with tumor histologically confined to the substance of the prostate. Other authors (4) have confirmed that capsular invasion alone in the radical prostatectomy specimen is not particularly adverse prognostically. Microscopic tumor invasion into the seminal vesicles of the radical prostatectomy specimen is an ominous finding in our experience and in the reported experience of many other authors. One-half of our patients with seminal vesicle invasion had tumor recurrence within 5 years of radical prostatectomy. Fortunately, when pelvic lymph nodes are negative, seminal vesicle invasion by prostatic tumor is uncommon; in our series (3), it was 6.5%.

Thus patients with positive nodes benefit little from radical prostatectomy, but those with localized tumor and negative nodes have a promising outlook. Further follow-up is needed in our radical prostatectomy series, but clearly, pelvic lymphadenectomy has been vital in the selection of appropriate candidates for radical surgery. Nodal assessment by lymphangiography, ultrasound, computed tomography scanning, and magnetic resonance imaging is not sufficiently accurate, even with fine-needle aspiration of suspicious lesions, to replace pelvic lymphadenectomy for reliable staging (5).

INFLUENCE OF STAGE AND GRADE ON PELVIC NODE INVOLVEMENT

The incidence of positive pelvic lymph nodes relates to clinical stage and tumor grade (table 2). We have reported 452 staging pelvic lymphadenectomies for clinically localized prostate cancer (6). None of 41 patients with stage A1 prostate cancer or minimal focal microscopic tumor had

¹ Division of Urology, Department of Surgery, University of Utah School of Medicine, 50 North Medical Dr., Salt Lake City, UT 84132.

TABLE 1.—Radical prostatectomy in patients with negative pelvic lymph nodes and 5-yr survival

Clinical stage	Total No. of patients	No. of patients alive at 5 yr			
		Total No.	Percent	No evidence of recurrence ^a	
				No.	Percent
A2	34	33	97	31	91
B1	44	43	98	40	91
B2	58	52	90	47	81
Total	136	128	94	118	87

^a Percentages represent No. of patients free of disease/total No. of patients.

positive pelvic nodes. For stage A2 tumor (diffuse microscopic prostate cancer), no low-grade tumors were associated with positive nodes, but 26% of the patients with moderately differentiated lesions and 43% with high-grade tumors had positive pelvic lymph nodes. Few of the patients, only 4%, with low-grade B1 tumor nodules had positive pelvic nodes, but an increasing incidence of nodal metastasis occurred with moderate- and high-grade B1 tumors. Not surprisingly, the incidence of positive nodes is higher in B2 tumors than in B1 nodules, and tumor grade is an important factor. More than one-half of the patients with clinical stage C prostate cancer had positive pelvic lymph nodes, and virtually all of those with poorly differentiated stage C lesions had nodal metastasis.

When radical prostatectomy for cure is considered, patients with clinical stages A2 and B2 tumors require a staging pelvic lymphadenectomy. Patients with low-grade B1 tumors have a low incidence of positive nodes, and it appears that lymphadenectomy is optional and nonessential. No need is indicated for pelvic lymphadenectomy in stage A1 prostate cancer, and I believe there is no need for treatment of any kind. Patients with clinical stage C prostate cancer are poor candidates for radical prostatectomy because it is almost certain that the tumor will be incompletely removed. Pelvic lymph node dissection may have value for staging if radiation treatment is contemplated in clinical stage C disease.

NODE DISSECTION WITH RADIATION THERAPY

The emphasis of this report is on pelvic lymph node dissection and radical prostatectomy. The place of node dissection in association with radiation therapy depends considerably on the philosophy of those who manage the treatment. If a patient with localized cancer (stages A2, B, and C lesions) has a negative pelvic lymphadenectomy, radiation therapy should be directed to the prostate and periprostatic area only. There seems to be no need for the radiologist to direct radiation therapy to the site of negative pelvic lymph nodes. Furthermore, node dissection followed by full pelvic irradiation produces a high incidence of chronic lymphedema of the legs and genitalia.

Many, probably most, radiation therapists treat localized prostate cancer by full pelvic irradiation with an extra boost of radiation energy to the prostate. If the full pelvis is to be irradiated, whether the lymph nodes in the pelvis are positive or negative, the lymphadenectomy is not crucial and should be avoided. However, we have a continuing problem in comparing the results of radical prostatectomy with those of radiation therapy for localized prostate cancer when only the patients who have radical prostatectomy have staging pelvic lymphadenectomy and a radical prostatectomy specimen to be examined histologically.

MORBIDITY OF PELVIC LYMPHADENECTOMY

Most often, pelvic lymphadenectomy is performed prior to radical prostatectomy, so separation of the morbidity associated with the node dissection from that relating to the removal of the prostate would be difficult. However, table 3 shows the morbidity in 176 patients who had pelvic lymphadenectomies performed as an independent staging procedure. Complications occurred in 9% of the patients. However, there were no fatalities, and only 1 patient with a ureteral injury required a reoperation.

CONCLUSIONS

Extensive experience with pelvic lymphadenectomy has led to the following conclusions:

- 1) Pelvic lymphadenectomy for staging is important prior to radical prostatectomy in patients with clinical stages A2 and B tumors, except for low-grade B1 lesions.

TABLE 2.—Incidence of pelvic lymph node metastasis by clinical stage and histologic grade^a

Stage	Grade							
	Well differentiated		Moderately differentiated		Poorly differentiated		Total	
	No./total	Percent	No./total	Percent	No./total	Percent	No.	Percent
A1	0/28		0/12		0/1		0/41	
A2	0/7		5/19	26	3/7	43	8/33	24
B1	2/53	4	13/94	14	3/9	33	18/156	12
B2	5/27	18	29/106	27	9/21	43	43/154	28
C	5/10	50	18/44	41	13/14	93	36/68	53
Total	12/125	10	65/275	24	28/52	54	105/452	23

^a Values = No. of patients who had metastases/total No. who had lymphadenectomies performed.

TABLE 3.—Complications of staging pelvic lymphadenectomy in 176 patients

Complication	No. of patients
Mortality	0
Morbidity	16 (9%)
Thrombophlebitis	4
Lymphocele	4
Retroperitoneal hemorrhage	1
Pulmonary embolus	3
Ureteral injury	1
Wound hematoma	3

- 2) If nodal metastasis is detected, radical prostatectomy is unlikely to be beneficial to the patient.
- 3) For staging, noninvasive techniques are not as accurate as pelvic lymph node dissection.
- 4) Some morbidity associated with pelvic lymphadenectomy is acceptable when accuracy of node staging is vital.
- 5) The role of pelvic lymphadenectomy prior to

external-beam radiation therapy depends on the physician's treatment philosophy.

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II. Radiation Therapy

Status of Radiation Treatment of Prostate Cancer at Stanford University

Malcolm A. Bagshaw,^{1,*} Richard S. Cox,¹ Gordon R. Ray²

ABSTRACT—Over 900 patients have been treated with radiation therapy in the 30-year Stanford prostate study. Overall survival, i.e., scoring death due to all causes, was 45%, 35%, 33%, 20%, and 10% for Stanford stages T0, T1, T2, T3, and T4 (nominal stages A, B1, B2, C) at 15 years; lymph node status was unknown. Disease-specific survival at 15 years was 85%, 64%, 45%, 33%, and 15%, respectively, for the same patients. In 141 patients with restricted nodular disease (lymph node status unknown) equal to or less than one-half of one lobe involved (stage B1), the 15-year overall survival was 50% and identical to the expected survival of an age-matched cohort of males. Potency was preserved in 86% of the patients at 15 months posttreatment, and 50% of the patients maintained erectile potency for 7 years posttherapy. Other sequelae and complications are analyzed. The incidence of second neoplasms did not exceed expectations for an age-matched population.—NCI Monogr 7:47–60, 1988.

External-beam irradiation for the treatment of prostate cancer was developed in the post-World War II era, and since then, case selection, technique, the risks, and expectations of this treatment method have been studied extensively (1–10). The details of this report are based upon the Stanford experience, which spans 3 decades and appears to be a fair representation of this overall experience.

PATIENTS AND METHODS

Between 1956 and 1985, 1,877 patients with adenocarcinoma of the prostate were referred for treatment (table 1). All patients were completely evaluated at the time of accession to the series, and physicians used a variety of techniques contemporary with the times to establish the extent of disease. Initially, the metastatic process was evaluated by roentgenographic surveys; later, x-ray films were replaced by state-of-the-art scintiscans of the skeleton.

Frequently lymphangiography, computed tomography, and, more recently, magnetic resonance imaging have been used as well. Of all the patients referred, 914 patients were selected for definitive treatment.

Treatment.—Although the patients described here were treated with 4- or 6-MeV x-rays, 6- and 15-MeV x-rays generated by linear accelerators are currently used. Un-

favorable rectal and bone sequelae are substantially reduced by a 4-field technique (fig. 1) incorporating parallel-opposed anterior and posterior and left and right lateral fields (fig. 2). This arrangement provides significant protection to the posterior wall of the rectum and avoids hot spots in bone. After 2,600 rad have been administered by the 4-field box technique, the radiation target is reduced to a coned down volume (fig. 3) for delivery of a booster dose of 2,000 rad limited to the prostate and seminal vesicles. Then the treatment program is expanded to the original 4-field box, which includes the entire first-echelon lymphatic system of the prostate. The composite distribution of radiation dose for the anterior, posterior, right and left lateral, and the left and right booster fields is depicted in figure 4. The radiation dose is delivered at the rate of 180 to 200 rad/day. This results in an absorbed dose of 7,000 rad in 7 weeks to the prostate, and 5,000 rad in 7 weeks to the first-echelon lymphatics. This program has been extremely well tolerated with only a rare instance of significantly symptomatic prolonged urinary tract or gastrointestinal morbidity.

Figure 5 demonstrates the age distribution that ranged from 35 to 86 years. The mean age was 63.4 and the median was 64 years. The series is neither prospective nor retrospective, but rather it is a continuing and contemporary study of the radiotherapy of prostate cancer as seen in the Department of Radiation Oncology at Stanford University.

Appropriate demographic, diagnostic, therapeutic, and follow-up items are systematically recorded and stored in a comprehensive data bank. Follow-up evaluation of about three-quarters of the patients is conducted in-house by the author, and the remainder of the patients and/or their referring physicians are interrogated regularly by a standard letter of inquiry or by telephone.

Staging system.—The Stanford TNM staging system was developed of necessity in the early 1970s before other TNM systems were generally available (11–13). Even though this is a parochial system, it is necessary that we review it briefly in order to clarify data to be presented later. This system defined the primary tumor with respect to local extent and identified several categories of apparent nodular disease in terms that might serve to define criteria for either resection or irradiation. It was based upon interpretations of Jewett's concepts, as published in his classic papers on the palpable nodule of prostate cancer (14). The original Stanford TNM system is presented in table 2. At the extremes, the T categories included TX, or status postsurgical resection, and T4, massive local tumor extending to the bony pelvis or invading adjacent organs. The intermediate T categories included cancer discovered coincident to a TURP (incidental), and this was further subdivided into T0f or T0d. The T1 included nodular neoplasm clearly confined to within the capsule. This stage was divided into 4 subgroups: T1a,

ABBREVIATIONS: MeV = million electron volt(s); TNM = tumor, node, metastases; TURP = transurethral resection of the prostate; T0f = cancer staging, focal subcategory; T0d = diffuse subcategory.

¹ Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA.

² Palo Alto Medical Foundation, Palo Alto, CA.

* Reprint requests to: Malcolm A. Bagshaw, M.D., Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA 94305.

TABLE 1.—Referrals for treatment of prostate carcinoma, October 1956 to December 1985^a

Total referrals		1,877
Exclusions		
Consultation only	198	
Metastatic disease	533	
Subtotal		731
Other		
Second primary tumor	64	
Prostatectomy	38	
Unusual primary tumor	5	
Previous irradiation	10	
Incomplete radiotherapy	14	
Questionable histology	4	
Implants	97	
Subtotal		232
Total exclusions		963
Treated by external-beam irradiation		
Disease limited to prostate	506	
Extracapsular extension	408	
Total No. of patients treated		914 (in study)

^a Patients were treated in the Division of Radiation Therapy, Stanford University Hospital.

a nodule 1 cm or a little more in diameter; T1b, a nodule occupying at least one-half of one lobe; T1c, a nodule occupying more than one-half but still limited to one lobe; and T1d, involvement of both lobes. The T2 category was purposely defined as borderline between intracapsular and extracapsular disease. This was an equivocal category, which included nodular lesions that distorted anatomic boundaries but did not definitely obliterate either the lateral sulci or the seminal vesicles. Stage T3 included tumors that clearly extended beyond the capsule, although they might involve less than 50% of a lobe or involve both lobes. Definitions of the various lymph node categories and metastatic sites are given in the table.

Throughout the study, a number of parameters were analyzed and the status of each patient was evaluated repeatedly. These observations included age, stage, histopathologic grade, treatment sequelae or complications, survival, disease-specific survival, freedom from relapse, and local control. Other items, such as lymphangiographic status or lymph node biopsy results, were also available for selected cohorts.

Statistical data.—Actuarial curves for the various patient groups were calculated by the method of Kaplan and Meier (15). For these calculations, patients were considered to be at risk from the initial date of radiotherapy. Various actuarial functions, as defined herein, were determined and these are presented.

- 1) Survival: Patients who die of any cause are regarded as failing at the time of death. Living patients are censored at the time of last follow-up and continue in the study.
- 2) Disease-specific survival: Patients who die of prostate cancer are regarded as failing at the time of death. Living patients are censored at the time of last follow-up; also, patients who die of intercurrent causes are censored at the time of death.

3) Freedom from relapse: Patients who relapse either at the primary site or at a metastatic site are regarded as failing at the time of first relapse. Patients who never relapse are censored at the time of last follow-up or intercurrent death.

4) Freedom from local relapse (local control): Patients who relapse at the primary site, as determined by clinical examination, are regarded as failing at the time of local relapse. Patients who never relapse locally are censored at the time of last follow-up or death.

5) Freedom from distant relapse: Patients who relapse at a metastatic site are regarded as failing at the time of metastatic relapse. Patients whose cancers never metastasize are censored at the time of last follow-up or death. No curves in this category are presented here, but the data exist and are accessible.

The significance of differences between actuarial curves was assessed by the generalized Wilcoxon test of Gehan (16).

The patients were first segregated according to the 12 groupings of the staging system. Actuarial survival curves were generated and Gehan *P* values were determined for successive pairs. Curves not separated by significant *P* values were coalesced, which resulted in a family of curves for each end point that remarkably, and with only one or two exceptions, grouped the patients into patterns that were originally predicted by the T stages. The method of grouping is shown in figure 6.

RESULTS

Patients with T0f (A1) and T0d (A2) incidental carcinoma are presented. Although the survival curves for T0f and T0d appear divergent, the *P* value fails to demonstrate a significant difference. Note also that the apparent difference between T0f and T0d virtually disappears when the end point is disease-specific survival rather than overall survival. This is because 17 or 35% of the patients with T0d (A2) died of intercurrent disease apparently without tumor, whereas only 4 or 8% of the T0d patients died of tumor. Two of 20, or 10% of the T0f (A1), patients died of tumor, and only 5 of 20 or 10.2% of them died of intercurrent disease. Therefore, the actuarial data for survival for T0f and T0d (A1 and A2) were pooled because the difference between like curves was not significant. Note also that the pressure of intercurrent death confounded the interpretation of mortality data in this group of elderly patients who, albeit elderly, still had an opportunity for long survival. Figure 7 shows the survival and disease-free survival patterns for these patients after the curves for focal and diffuse disease were coalesced.

Figure 8 demonstrates the overall actuarial survival of all patients as a function of the Stanford T-staging system. Note that, although adenopathy was known for a few patients, it was not known for all and, therefore, in this and later figures, the status of adenopathy was disregarded as a staging parameter. However, in a previous study, surgical assessment of lymphadenopathy in a cohort of these patients demonstrated histopathologically positive lymph nodes in 19% of the T1 and T2 (stage B), and 56% of



FIGURE 1.—Parallel-opposed anterior and posterior fields in the 4-field treatment technique.



FIGURE 2.—Left and right lateral fields in the 4-field treatment technique.

the T3 (stage C) patients (11). Of the T stages, T1, intracapsular, and T2, equivocal (curves 1 and 2), behaved identically in overall survival. These two curves might have been coalesced; however, we purposely displayed them individually to provide an easy comparison with the same stages to be displayed next as a function of disease-specific survival. From the standpoint of overall survival, little difference appeared between patients with small nodules and those with extensive intracapsular involvement. Later data, however, will show that within the finer subgrouping of T1, there were significant differences in favor of lesser disease. Again, the pressure of intercurrent death tended to obfuscate the true number of deaths caused by prostate cancer when overall survival was viewed.

However, the disease-specific survival displayed in figure 9 demonstrated a nearly significant difference between those with T1 or definitive intracapsular disease and those with T2 or equivocal capsular disease ($P = .07$). This difference shows that when the capsule was distorted (T2), the disease-specific survival pattern was somewhere between T1 and T3, in keeping with the ambiguity built into the definition of the T2 category.

Figure 10 depicts the pattern of freedom from relapse as a function of T stage. In this situation, the patient was scored as demonstrating no clinical evidence of disease if 1) upon physical examination, no evidence of tumor regrowth was observed on rectal examination following a prior regression after radiation therapy, and 2) routine ancillary examinations, such as acid phosphatase determinations, bone scans, or roentgenograms, failed to reveal a neoplasm. Recently, prostate-specific antibody determinations

have been added as a surveillance marker. This evaluation did not include routine biopsy of the primary site. Reference to the table of P values in figure 10 segregates patients at least according to T stage into 5 highly significant groups. Therefore, freedom from relapse was the end point that most sharply defined the long-term outcome of the radiation treatment of prostate cancer as a function of T stage. Clearly, as with most types of cancer, prostate cancer becomes progressively more difficult to control as the T stage escalates. Also, because tumor volume appears to be the dominant factor in the definition of T stage, tumor mass and presumably the cell number appear to play the most significant role in the determination of radiocurability.

Figure 11 presents an actuarial analysis of control of tumor at the primary site (local control) as a function of T stage. Local control was determined by physical examination only and, therefore, to a certain extent lacked authority. Some of the patients were known to have had positive biopsies at the primary site, but these were disregarded in this analysis because only a minority of the patients were submitted to biopsy, and in some of them, the clonogenicity of the apparently positive biopsies was in doubt. Clinical local control appears to be a considerably less reliable end point than either disease-specific or relapse-free survival. Local control does not clearly segregate the patients into reasonable stages.

One concept of the initial Stanford staging system was to isolate solitary nodular disease as had been suggested by Jewett et al. (14). The T1 category was comprised of nodular carcinomas which were, as near as could be determined by physical examination, unequivocally confined within the

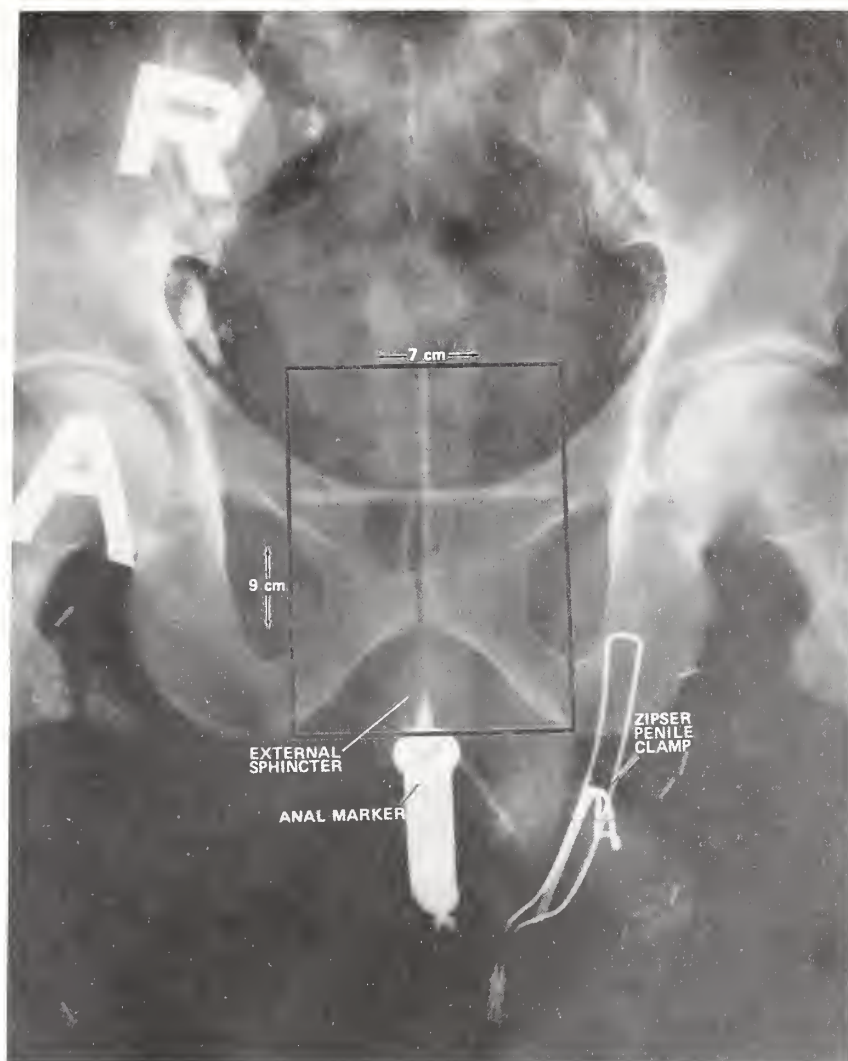


FIGURE 3.—Coned down volume for delivery of radiation booster dose to the prostate and seminal vesicles.

prostate. The T1a nodule included those up to 1 cm or a little more in diameter, the T1b those that were larger than T1a but equal to or smaller than one-half of one lobe (2 to 2.4 cm in diameter), the T1c those that occupied either an entire lobe or were multiple but confined to one lobe, and the T1d those that occupied a portion of both lobes or the entire gland. Inspection of figure 12 tells one that there was no significant difference in the probability of survival between stages T1a and T1b and, similarly, no significant difference in survival between T1c and T1d. Therefore, on combining the like substages in T1, the survival pattern is as depicted in figure 13. The survival pattern for intracapsular nodular carcinoma of the prostate up to nodules at least equal in size to one-half of one lobe following irradiation appears identical to the expected survival of an age-matched population of males and is highly significantly better than for the larger lesions, even though the larger ones still might be presumed to be confined within the capsule. As stated above, disease-specific survival is perhaps a more informative way for one to view outcome in prostate cancer, inasmuch as the confounding influence of death due

to intercurrent disease is removed. Disease-specific survival is presented in figure 14 for the T1 lesions. At 15 years, it is essentially 80% for T1a and T1b lesions and 50% for T1c and T1d tumors. Although some might consider this T1b carcinoma of the prostate to be a small nodule, this is only relative. For example, if one considers a normal prostate to weigh about 30 g, then a nodule occupying about one-half of one lobe would be approximately 7.5 g or it would be a nodule of about 2.4 cm in diameter. This is a sizable nodule when one considers the work of McNeal et al. (17), in which 7 of 9 prostate cancer specimens of 5.4 ml or larger had at least 1 cm of complete (level III) capsular penetration, and 6 of 7 had seminal vesicle invasion.

Postradiotherapy Biopsy

Table 3 demonstrates that 64 of 146 patients who were surgically staged for evaluation of adenopathy at Stanford had posttherapeutic biopsies on an ad hoc basis 2 years or longer following irradiation. The incidence of positive biopsies increased with increasing clinical stage. Table 4

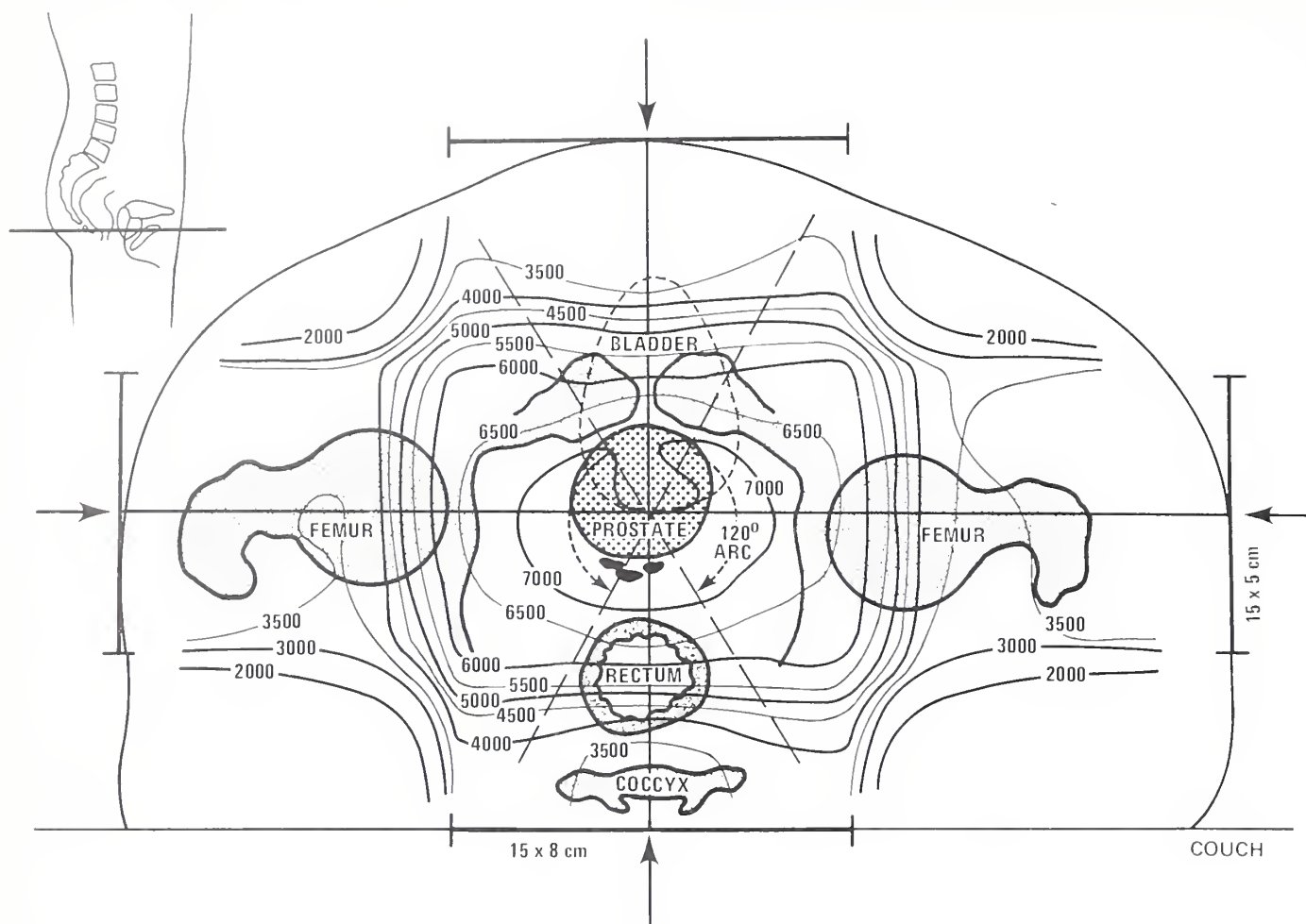


FIGURE 4.—Composite isodose distribution of the radiation dose, taken at the level of the prostate.

shows that among the 39 patients who had positive biopsies, 8 were living with metastatic disease, and 18 subsequently died of progressive disease. Eleven others had positive biopsies, but 10 have manifested no further progression. Therefore, it is apparent that conventional megavoltage ir-

radiation in doses as high as 7,000 rad in 7 weeks, as was used in these patients, was frequently incapable of sterilizing primary prostate carcinoma, particularly in the more bulky stage T2 (B2) and T3 (C) lesions.

Conversely, however, the neoplasm was sterilized in many patients, and ways to improve the ability to achieve local control at the primary site are available, one of which is to boost external-beam irradiation with transperineal iridium-192 interstitial implants, as has been advocated by Syed et al. (18) and also by the Stanford group (fig. 15). Both use a perineal template designed to place interstitial iridium implants directly into the primary in stage C tumors.³ Other booster methods being tested include the use of high-energy protons, neutron irradiation, negative pion meson irradiation, and heavy-ion irradiation. The addition of hyperthermia to either external-beam or interstitial irradiation also may improve local control. Future studies may

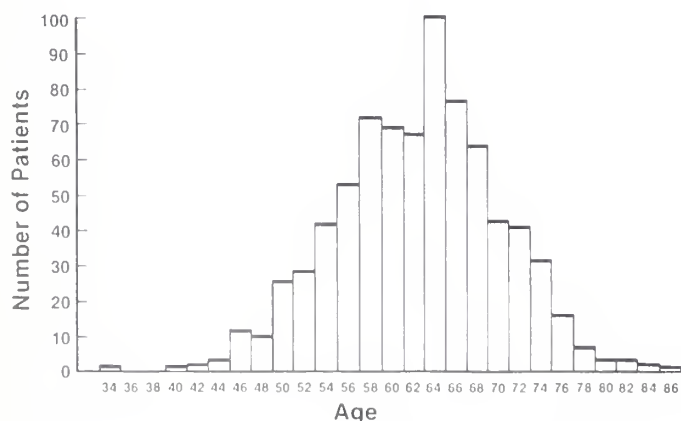


FIGURE 5.—Age distribution of patients with prostate cancer at the time of referral to Stanford. Mean age = 63 yr.

³ As described above, 5,000 rad are delivered in 5-6 weeks to the prostatic region with the 4-field technique. Then the patient is allowed 4 weeks of rest, followed by an interstitial iridium-192 implant that adds a 3,000-rad boost to the primary site.

TABLE 2.—Clinical staging system for prostate cancer

T staging: Primary tumor

TX: Characteristic anatomic relationships distorted and/or absent secondary to major surgical intervention, i.e., radical prostatectomy.

T0: Occult carcinoma; incidental finding of carcinoma in the operative specimen following TURP.

f: focal = less than 5% of specimen.

d: diffuse = more than 5% of specimen.

T1: Palpable tumor limited by the prostatic capsule without distortion of the superior or lateral anatomic boundaries.

a: Solitary nodule ≤ 1 cm in diameter with normal, compressible prostatic tissue on three sides (lesion amenable to radical prostatectomy).

b: Palpable tumor > 1 cm occupying less than 50% of a lobe.

c: Palpable tumor occupying $> 50\%$ of a lobe, multiple nodules limited to one lobe.

d: Involvement of both lobes.

T2: Palpable tumor of any size primarily limited by the prostatic capsule with minimal distortion of the lateral or superior anatomic boundaries *without definite* obliteration of a lateral sulcus and/or a seminal vesicle region.

a: Palpable tumor occupying up to 50% of one lobe.

b: Palpable tumor occupying $> 50\%$ of a lobe, multiple nodules limited to one lobe, or involvement of both lobes.

T3: Palpable tumor extending beyond the prostatic capsule with definite obliteration of any extent of a lateral sulcus and/or a seminal vesicle region.

a: Palpable tumor occupying up to 50% of a lobe.

b: Palpable tumor occupying $> 50\%$ of a lobe, multiple nodules limited to one lobe, or involvement of both lobes.

T4: Palpable tumor extending beyond the prostatic capsule with attachment to both pelvic sidewalls, rectal wall invasion, or bladder invasion.^a

N categories: Nodes

Nodal designations will involve two notations: N _____. The first blank designates the *clinical impression*; the second blank designates the *biopsy status*.

Clinical:

X: Lymphangiogram not performed or technically inadequate.

0: Lymphangiogram not consistent with carcinomatous involvement of either the regional or para-aortic nodes.

1: Lymphangiogram consistent with carcinomatous involvement of the regional nodes; para-aortic nodes uninvolved.

2: Lymphangiogram consistent with carcinomatous involvement of the para-aortic nodes; regional nodes uninvolved.

3: Lymphangiogram consistent with carcinomatous involvement of the regional and para-aortic nodes.

4: Pathologic adenopathy of other than regional or para-aortic nodes, as demonstrated by lymphangiography, chest x-ray, or physical examination; e.g., supraclavicular, mediastinal. (If biopsy is not performed and is negative, disregard this category.)

Biopsy:

x: Biopsy not performed or technically inadequate.

a: No evidence of tumor in regional and para-aortic nodes.

b: Regional nodes positive, para-aortic nodes negative for tumor.

c: Regional nodes negative, para-aortic nodes positive for tumor.

d: Regional and para-aortic nodes positive for tumor.

e: Any of the aforementioned plus positive biopsy of nodal site outside regional or para-aortic nodes. (If not biopsied, place x.)

M sites: Distant metastases (excluding lymph nodes)

M0: No evidence of metastases.

M1: Isolated area of abnormal epithelial cells in bone marrow unassociated with multiple bony, soft tissue, or visceral metastases.

M2: Bony, visceral, or soft tissue metastases with or without bone marrow involvement.

Example:

The stage of a patient who has 25% of one lobe involved with tumor and invasion of the right seminal vesicle, who had a lymphangiogram that shows normal regional and para-aortic nodes, and a biopsy that reveals tumor in the regional nodes and negative para-aortic nodes but evidence of metastases would be 3aN0bM0.

^a Patients with intravenous pyelogram findings suggestive of bladder involvement will undergo cystoscopy and biopsy if indicated.

show that nearly all of these methods can be augmented further by the use of radiosensitizers.

Radiation Sequelae

Mild symptoms of urinary frequency or urgency, nocturia, or diarrhea occur in about 50% of the patients during the course of irradiation. Symptoms that persisted for more than 2 years or severe transient symptoms that required surgical intervention are tabulated in table 5.

The analysis of sequelae was complicated by two issues. Between 1956 and 1985, of the 893 patients who were treated and analyzed for complications, 91 were par-

ticipants in a protocol study that required transperitoneal biopsy of the pelvic and para-aortic lymph nodes as a staging procedure. This yielded valuable information on the incidence of para-aortic lymph node metastases; however, it became apparent that the transperitoneal approach to the para-aortic lymph nodes, combined with para-aortic radiation therapy (which in some patients amounted to 5,500 rad), caused excessive morbidity. For example, a substantially higher incidence of small bowel damage requiring surgical correction occurred in this selected cohort (19). As a result, the transperitoneal approach was abandoned in favor of retroperitoneal limited node sampling in appropriate cases, and the para-aortic radiation dose was reduced

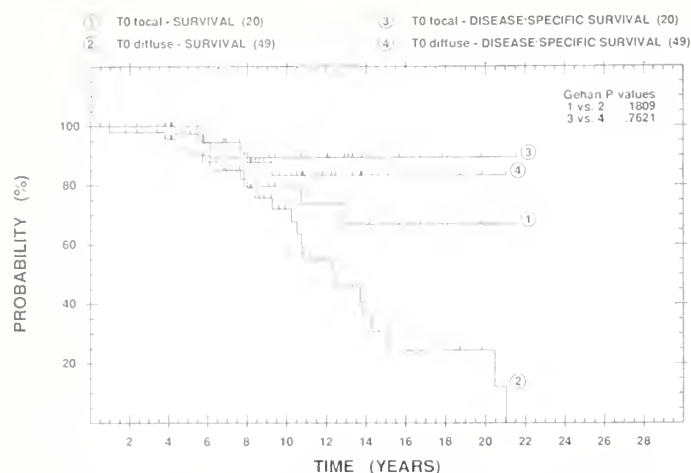


FIGURE 6.—Survival and disease-specific survival, i.e., death due to prostate cancer only (node status unknown), for incidental T0f and T0d (A1 and A2) carcinoma of the prostate.

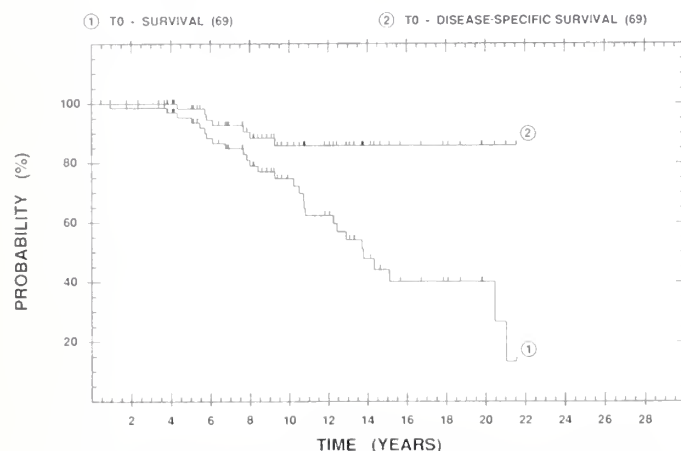
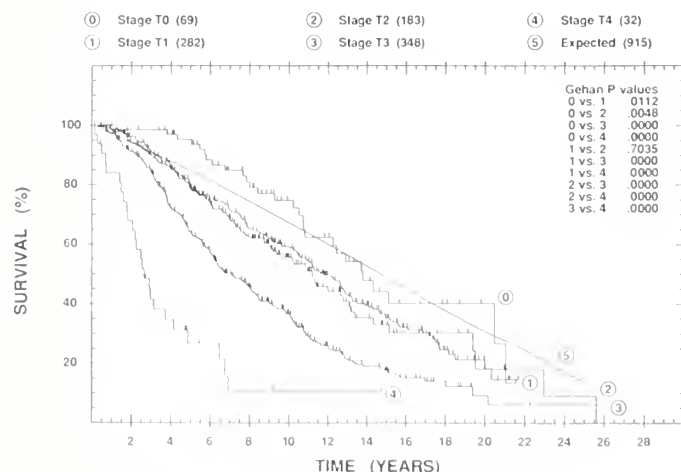


FIGURE 7.—Survival and disease-specific survival for T0, incidental, carcinoma of the prostate (node status unknown) after coalescing the statistically similar curves for focal and diffuse disease.



FIGURES 8–14.—Prostate cancer, node status unknown.

FIGURE 8.—Survival. A downward step represents death due to any cause. An upward tick represents a patient surviving at last follow-up and censored at the time indicated by the abscissa. Patient may or may not have residual or metastatic cancer.

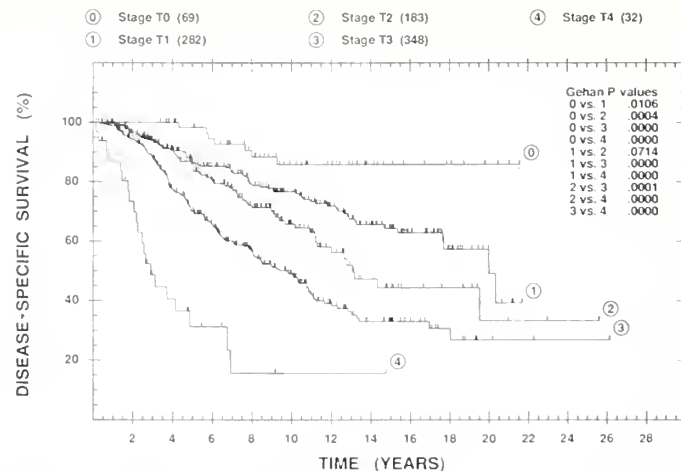


FIGURE 9.—Disease-specific survival. A downward step indicates death due to prostate cancer. An upward tick represents a patient who 1) died due to intercurrent disease, or 2) was alive at the time of last follow-up; patient may or may not have cancer.

to 5,000 rad in 5 weeks. In table 5, the radiation sequelae are presented in 2 groups: 802 patients who did not have transperitoneal lymph node biopsy, and 91 patients with excessive morbidity on whom a celiotomy had been performed. Note the striking difference in the complication rate between the 2 groups, particularly with respect to intestinal damage and lower extremity or genital edema. The other factor that confounded the true incidence of radiation sequelae in these patients was the frequent inability of investigators to determine whether a given severe, persistent abnormality was due to persistent tumor or to radiation effect. For instance, rectal obstruction in several instances has appeared to be caused by extensive local tumor growth. However, we made no attempt to distinguish between the symptoms caused by tumor and those caused by the treat-

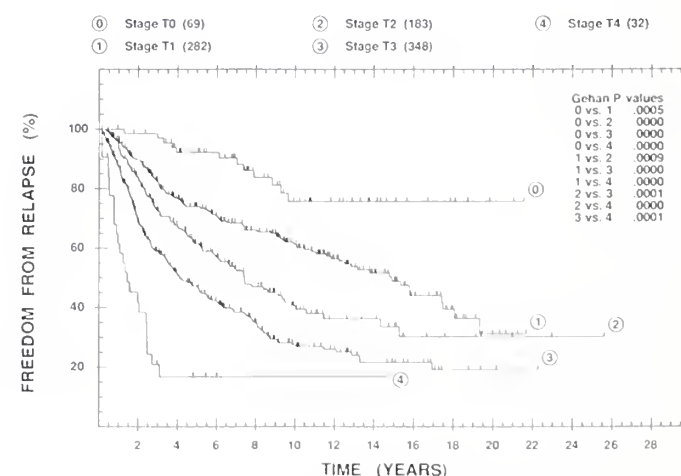


FIGURE 10.—Freedom from relapse. A downward step indicates the first evidence of recurrence, either at the primary site or at a metastatic site as detected by either clinical observation or by a positive biopsy. An upward tick represents a patient who was either observed disease free or died disease free at the time of last observation.

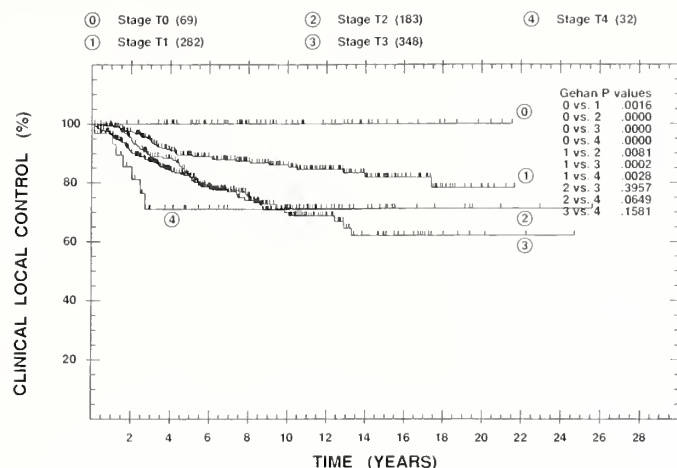


FIGURE 11.—Local control. A downward step indicates clinical evidence of local regrowth after initial regression of tumor or after initially showing no evidence of local neoplasm. An upward tick represents a patient who demonstrated 1) no clinical evidence of local tumor at last follow-up, or 2) died without clinical evidence of local neoplasm. Patient could have had evidence of metastatic tumor either while living or at death.

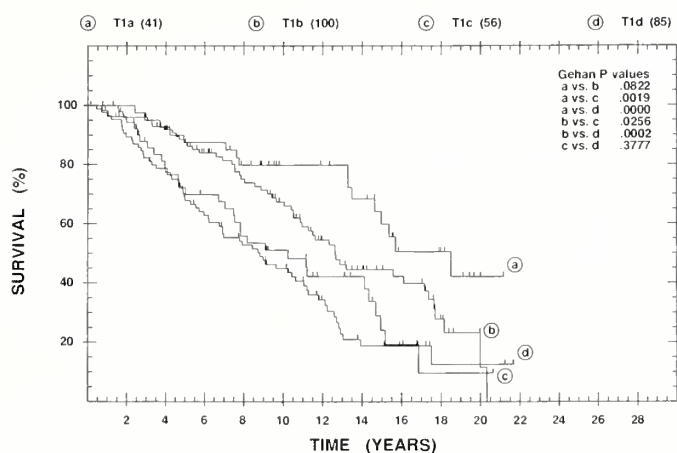


FIGURE 12.—A family of survival curves for T1 (intracapsular) carcinoma of the prostate is demonstrated. (See table 2 for precise definitions of the substages.)

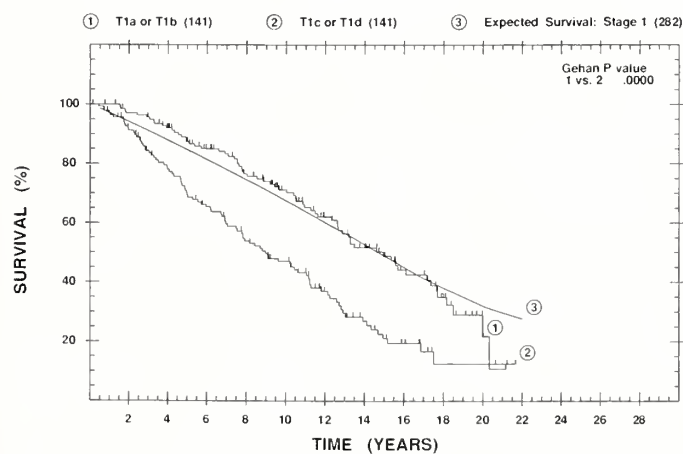


FIGURE 13.—Statistically similar subgroups of stage T1 (intracapsular) carcinoma of the prostate are coalesced.

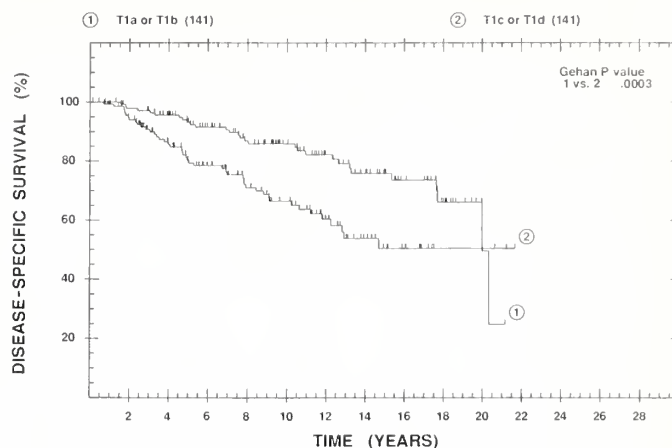


FIGURE 14.—Disease-specific survival for the T1 lesions.

ment, and all sequelae are enumerated whether due to radiation exposure or persistent neoplasm.

In table 6 are the results of the nonprotocol patients who were examined with reference to the period during which the radiotherapy was administered. It has been the impression that the incidence and severity of radiation sequelae have declined in recent years. This reduction correlates well with, among other things, the introduction in 1974 of the midcourse prostatic radiation boost, first suggested by S. Weller (personal communication). The table demonstrates that from January 1965 through December 1974, 431 patients were treated, and the incidence and severity of radiation sequelae during that period were compared with the same factors observed for the 289 patients treated between January 1975 and December 1984. Inspection of table 6

TABLE 3.—Results of biopsy according to stage of primary tumor^a

Stage	No.	Positive biopsy	
		No.	Percent
A2	1	0	0
B1	2	0	0
Small B2	8	3	38
Large B2	22	13	59
C	31	23	74
Total	64	39	61

^a Chi-square = 4.732; $P = .030$. From 146 staged patients on whom laparotomies were performed, we selected 64 ad hoc for transperineal prostatic biopsy 2 yr or longer following external-beam irradiation.

TABLE 4.—Current status of 64 patients

Status	Positive biopsy	Negative biopsy
Alive without metastases or progression	11 ^a	19
Alive with metastases	8	3 ^b
Dead of progressive disease	18	3 ^b
Dead of other causes, with metastases	2	0

^a Of the 11 patients, 7 are on diethylstilbestrol for local control, and 2 have received interstitial irradiation.

^b Four of 6 patients had positive nodes at initial staging.



FIGURE 15.—Frontal radiograph showing intraprostatic alignment of trocars containing iridium-192 that have been introduced through a perineal template.

shows a statistically significant reduction in intestinal sequelae from 6.5% to 2.4% of the patients and a reduction in urologic sequelae from 10.9% to 7.2% of the patients during the most recent decade.

Status of Erectile Potency Following External-beam Irradiation

During this study, of the 434 patients who claimed erectile potency prior to irradiation, 86.4% remained potent at

15 months after the start of radiation therapy. Furthermore, although erectile potency diminished with advancing age, 50% of the patients remained potent at the seventh year following irradiation, and more than 30% maintained sexual performance for the duration of their survival (fig. 16).

Table 7 demonstrates that radiation therapy for prostate cancer does not induce an increased incidence of second neoplasms. Although 10.8% of the patients developed a

TABLE 5.—Radiation sequelae in patients with prostate cancer, September 1956 to December 1984^a

Type and/or cause of symptoms	Sequelae					
	Intestinal		Urologic		Other (edema)	
	No.	Percent	No.	Percent	No.	Percent
Nonprotocol patients (802)						
Persistent > 2 yr	30	3.7	51	6.4	12	1.5
Transient/severe (surgical)	6	0.7	25	3.1	2	0.2
Protocol patients (91; orchiectomy)						
Persistent > 2 yr	13	14.3	9	9.9	13	14.3
Transient/severe (surgical)	5	5.5	6	6.6	0	

^a Numbers in parentheses are numbers of patients in the group. Chi-square = 37.677; two-tailed $P = .000000$.

TABLE 6.—Radiation sequelae in nonprotocol patients with prostate cancer^a

Type and/or cause of symptoms	Sequelae					
	Intestinal		Urologic		Other (edema)	
	No.	Percent	No.	Percent	No.	Percent
Patient group ^b						
Persistent	22	5.1	33	7.7	7	1.6
Transient/severe	6	1.4	14	3.2	1	0.2
Patient group ^c						
Persistent	7	2.4	14	4.8	4	1.4
Transient/severe	0		7	2.4	1	0.3

^a Chi-square = 9.08; two-tailed $P = .0026$. Persistent refers to symptoms of >2-yr duration. Transient/severe refers to symptoms requiring hospitalization and surgical correction, e.g., TUR for obstructive symptoms.

^b From January 1965 through December 1974, 431 patients were treated.

^c Between January 1975 and December 1984, 289 patients were treated.

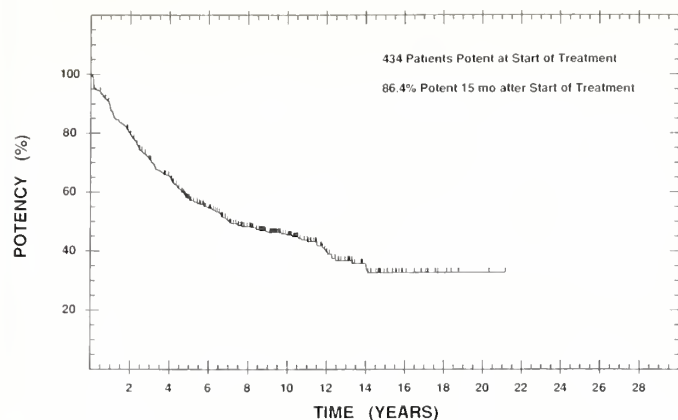


FIGURE 16.—Status of erectile potency after external-beam irradiation for prostate cancer (node status unknown).

second neoplasm, neither the incidence nor the spectrum deviated from expectations.

DISCUSSION

A comparison of long-term survival of the irradiated Stanford patients with the results following surgery in 2 well-documented series of patients treated by radical prostatectomy is illustrated in figure 17. Overall survival in the patients treated surgically at The Johns Hopkins Hospital (20) and the Virginia Mason Medical Center (21), and the patients in stages T1a and T1b treated at Stanford University Hospital did not deviate significantly from each other through 15 years of follow-up (fig. 17). Of course, there were differences in case selection as is inevitable when independent series are developed at different institutions during different times.

Time-to-first-evident metastasis in surgically staged patients, randomly allocated to either radical prostatectomy or definitive x-irradiation, was tested in the mid-1970s and reported by the Uro-Oncology Research Group in 1982 (22). Coincidentally, a group of patients at Stanford was

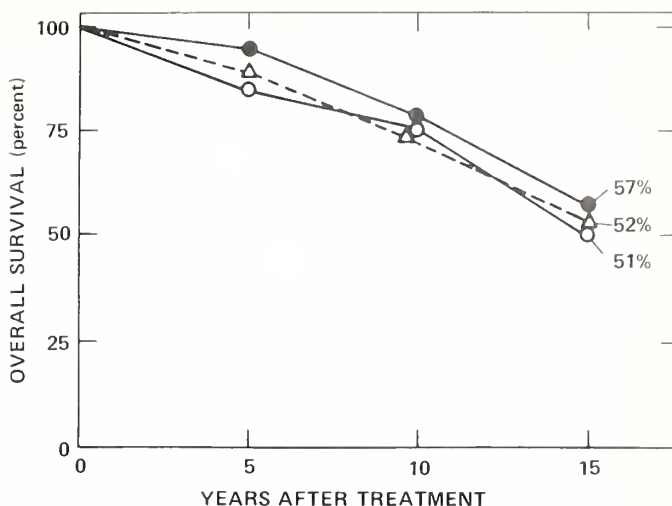


FIGURE 17.—Comparison of long-term survival of patients in stage T2a (B1) treated by radiation therapy in the Stanford University Hospital series (134 patients; open triangles) and those treated by radical prostatectomy in the series at The Johns Hopkins Hospital (57 patients; open circles) and Virginia Mason Medical Center (195 patients; solid circles) according to a personal communication (Shipley WU).

evaluated according to a nearly identical protocol, and all 51 patients clinically staged as A2 or B who had no lymphadenopathy as proved by surgical staging were treated with external-beam irradiation exactly as prescribed for the Veterans Administration radiotherapy group. The data from the Uro-Oncology Research Group (22) of the Veterans Administration and those from the Stanford study are plotted in figure 18. The pattern of treatment failure in the irradiated Stanford patients was nearly identical to that of the surgically resected patients and significantly better than that of those treated by irradiation in the Veterans Administration study. The 51 patients in the Stanford group are under continuing follow-up, and their recent status is demonstrated in figure 19, which shows a 60% survival at 13

TABLE 7.—Incidence of second cancers following prostate cancer^a

Type of second cancer	Observed	Expected	P
Lung	28	29.3	.81
Colon	15	15.2	.96
Bladder	11	10.2	.80
Stomach	6	5.4	.80
Rectum	4	7.4	.21
Leukemia	4	3.8	.92
Lymphoma	3	4.1	.65
Pancreas	3	4.6	.27
Kidney	1	2.9	.26
Other	24	—	—
Total ^b	99	106.2	.48

^a Observed second cancers vs. expected incidence was calculated by the method of Monson from the Surveillance, Epidemiology, and End Results Program data for Bay Area white males. There were 914 patients at risk for more than 7,000 person-yr.

^b Observed second cancers occurred in 10.8% of the prostate cancer patients.

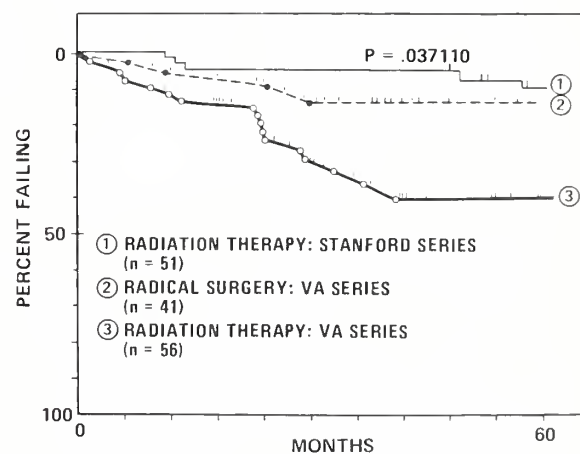


FIGURE 18.—Time-to-first evidence of treatment failure. Curve 1 is generated from the Stanford data and is superimposed [with the author's (22) permission] on the original figure from the Uro-Oncology Research Group study. The P value refers to curves 2 and 3 only.

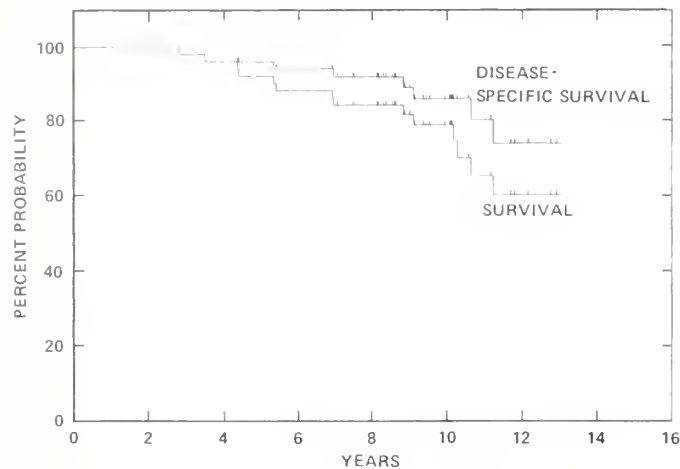


FIGURE 19.—Long-term, disease-specific, and overall survival of 51 patients in stages A2 and B prostate cancer who had no histopathologically positive lymph nodes at surgical staging (T0d, T1, T2, N0, and M0). These patients were staged between 1970 and 1978 and are under constant follow-up.

years and a disease-specific survival of 75% for the same interval.

From the above, expectation of a long-term difference in survival statistics between stages A and B1 patients treated by either radical resection or external-beam irradiation appears to have little precedent. What about more advanced carcinoma? The inaccuracy of clinical staging before surgical resection has long been a concern of thoughtful surgeons, but the *impact* of the true pathologic stage not being recognized prior to surgical resection has not been equally well appreciated. The rather complex data detailed in table 8 summarize reports that contain information on clinical understaging and, in some cases, its impact on postoperative survival (19,23-34). In each instance in which the impact on survival was stated, the long-term survival was reduced by more than 50% in patients who had a pathologically proven incomplete surgical resection.

Several authors (34-36) have demonstrated that residual tumor at the surgical margins appears amenable to sterilization by postprostatectomy irradiation. For example, in the Stanford series, a 57% long-term survival was achieved

TABLE 8.—Prostate cancer preoperative understaging^a

Study			Clinical stage		Pathologic capsular or extracapsular disease		Seminal vesicle invasion, %	Impact on survival at:		
								No. of years	Decrease in percent	
Year	Principal investigator	Reference	Stage	No.	No.	Percent			From	To
1953	Colby	(23)	B1 (exceeded expectation)		25	71	36	5	52	27
1957	Turner	(24)				45	—			—
1963	Vickery	(25)					47			—
1968	Culp	(26)				44	8			—
1972	Byar	(27)	B1 B2			11	12	5	58	33
1977	Dahl	(28)				22	—			—
1977	deVere White	(29)				29	—			—
1977	Boxer	(30)				29	—	10	62	29
1980	Walsh	(20)	B1				16			
			B2				49	15	51	5
1982	Elder	(31)	A2 ^c			66 ^b	13 (minimum)	15	50	13
1982	Catalona	(32)	B1			11 ^b	—			
			B2			17 ^b	—			
						39 ^b	—			^d
					Overall	24	—			No data
1982	Middleton	(33)	B2 ^c			12	4			—
1983	Lange	(34)	A2 ^f	6	3		3			
			B1	32	25	68	5			^g
			B2	25	15		9			
1984	Gibbons	(21)	B			25	—			—

^a Carcinoma was considered confined to the prostate prior to radical prostatectomy.

^b Patients had extracapsular disease.

^c Five patients had an early failure.

^d Follow up was short.

^e Clinical stage was node negative.

^f Of the 6 patients with this clinical stage, 3 had extracapsular disease, and the impact on survival was not stated.

^g Patients received x-ray therapy.

in 13 patients who were irradiated immediately following inadequate resection, whereas in 19 patients, a 20% long-term survival was achieved following definitive irradiation in the face of frank recurrence after prior prostatectomy. The suggestion by Stamey and co-workers (37) that the prostate-specific antigen may be a specific and sensitive marker for the determination of residual neoplasm or recurrence after prostatectomy is worthy of careful study because it might clearly identify a group of patients who would benefit from postoperative irradiation.

SUMMARY AND CONCLUSIONS

The interpretation of end results following various treatments for prostate cancer remains a confusing issue. Part of this is due to the lack of wide acceptance of a universal staging system, and part is due to a lack of definition and clarity on the selection of end-point parameters and their statistical presentation. In this paper, we have attempted to call attention to these deficiencies and to present clear alternatives. We hope that clarification of staging and end-point reporting will become the subject of continuing effort.

An actuarial survival (scoring death due to all causes) of 50% at 15 years has been achieved following external-beam irradiation in patients with early prostate cancer, i.e., T0, T1a, and T1b (stages A, A2, and B1). This is equal to the expected survival of an age-matched population and also equal to the survival rates reported in earlier surgical series of equal longevity. Thus surgical resection and radiation therapy as related to survival appear to be equal alternatives in early disease. Perhaps reasonable physicians should routinely disclose this fact to the beleaguered patients.

As stage and, consequently, tumor mass escalate, long-term survival following irradiation decreases; however, it still remains at 20% for T3 (stage C), and even at 10% for patients with massive T4 (stage D) local disease. Improvement in radiation therapy will require continuing development of adjunctive techniques for improving the efficacy of treatment. Methods, such as boosting the tumor dose with radioactive implants or high-energy particles or the addition of localized hyperthermia, hold promise for improving the sterilization of more advanced neoplasms. All of these methods could be enhanced by the development of an efficacious radiation sensitizer.

A more accurate pretherapeutic assessment of the precise extent of the primary neoplasm by an advanced imaging modality, such as ultrasound, magnetic resonance imaging, or spectroscopy, would be extremely valuable in matching patients to the appropriate treatment strategy.

Surgical transection of tumor that leaves residual neoplasm appears to be identifiable by an elevation of prostate-specific antigen titer. This could trigger the appropriate use of postoperative radiation therapy, which appears to be a safe and effective adjunct to surgery in this situation. A clinical trial that would establish this diagnostic and therapeutic combination seems warranted.

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Radiation Therapy Oncology Group Studies in Carcinoma of the Prostate

Miljenko V. Pilepich^{1,*}

ABSTRACT—From 1976 to 1983, the Radiation Therapy Oncology Group (RTOG) conducted 2 large-scale phase III trials of extended field irradiation in patients with carcinoma of the prostate. The first, RTOG 75-06, was designed to test the value of elective periaortic irradiation in patients in whom the tumor extended beyond the gland, but remained limited to the pelvis, and the second, RTOG 77-06, was designed to test the value of elective pelvic irradiation in patients without evidence of spread beyond the prostate. The results indicated no apparent benefit from elective periaortic irradiation in patients with detectable disease confined to the pelvis and no apparent benefit from elective pelvic irradiation in patients with detectable disease confined to the prostate. Patients with extracapsular extension of the primary tumor and evidence of pelvic lymph node involvement demonstrated an outcome comparable to that in patients without evidence of lymphatic involvement. This observation may reflect a beneficial effect of pelvic irradiation in patients with nodal involvement. In contradistinction to *elective* irradiation of regional lymphatics, *therapeutic* irradiation (of the involved lymphatics) may prove strongly indicated. A prospective study testing this contention needs to be conducted. No significant correlation of treatment-related morbidity and treatment volume could be identified. Analysis of the various types of treatment-related morbidity as to the time of onset and clinical course indicated that these behave as different disease entities characterized by a specific pattern of appearance, clinical course, and prognosis. Of particular interest is the observation that most appear reversible. Doses in excess of 7,000 cGy to the prostate were associated with a significantly increased incidence of bowel morbidity. Certain treatment techniques were also associated with a significantly increased incidence of treatment-related problems. Although patients who received concomitant hormonal management had a significantly higher proportion of high-grade lesions, their clinical course fared favorably in comparison with the population not receiving hormonal management. This apparent beneficial effect of adjuvant hormonal treatment needs to be tested in a prospective study.—NCI Monogr 7:61-65, 1988.

Since 1976, the RTOG has conducted a series of studies on carcinoma of the prostate. Between 1976 and 1983, emphasis was placed on 2 large-scale phase III trials aimed at the definition of an optimal treatment volume in patients with locally extensive disease (RTOG 75-06) and disease limited to the prostate (RTOG 77-06). Starting in 1981, a series of studies aimed at evaluation of adjuvant modalities was initiated. These included a study of adjuvant chemotherapy (RTOG 81-12) and a series of studies

aimed at evaluation of adjuvant endocrine management. These include phase II studies of hormonal cytorreduction before and during a course of radiotherapy (RTOG 83-07 and 85-19) and a phase III study of hormonal cytorreduction (RTOG 86-10).

The data accumulated on the first 2 studies (75-06 and 77-06) have matured sufficiently to provide a base for a series of analyses that will be summarized in this communication.

STUDY DESIGN AND POPULATION

The primary aim of those who designed the RTOG 75-06 was to test the value of periaortic irradiation in patients in whom there was evidence of tumor extension beyond the prostate, but limited to the pelvis. Patients with clinical stage C tumor were eligible whether or not pelvic lymph nodes were involved. For these patients, assessment of nodal status was optional. Patients with stage A2 and B were also eligible but only if they had either lymphangiographically or histologically confirmed pelvic lymph node involvement.

The stratification criteria included histologic grade, clinical stage, absence or presence of hormonal manipulation, and method of lymph node evaluation (lymphangiogram vs. laparotomy vs. no nodal evaluation). The patients were randomized to receive either pelvic irradiation followed by a boost to the prostate, or pelvic and periaortic irradiation followed by a boost to the prostate. The prescribed daily dose was 180–200 cGy to a total midplane dose to the regional lymphatics of 4,000–4,500 cGy. The prostatic boost target volume was to receive an additional 2,000–2,500 cGy, bringing the total dose to the area to a minimum of 6,500 cGy.

The end points of the study included an assessment of the effect of treatment arm assignment on disease-free survival, survival, and treatment-related morbidity.

The primary aim of those who designed RTOG 77-06 was to test the value of elective pelvic irradiation in patients without evidence of spread beyond the prostate. Eligible patients were those with clinical stages B and A2 without evidence of pelvic lymph node involvement by either lymphangiogram or laparotomy. Evaluation of the regional lymphatics was mandatory. Stratification criteria included histologic grade, absence or presence of hormonal manipulation, and method of nodal evaluation (laparotomy vs. lymphangiogram). The treatment entailed either irradiation of the pelvis followed by a prostate boost or prostatic irradiation only. The prostate was to receive a minimum of 6,500 cGy in 6½ to 7 weeks. In patients randomized to receive pelvic irradiation, the pelvis was to receive 4,500 to 5,000 cGy in 4½ to 5 weeks. The daily tumor dose was 180 to 200 cGy.

ABBREVIATION: RTOG = Radiation Therapy Oncology Group.

¹ Radiation Oncology Center, Washington University School of Medicine, St. Louis, MO.

* Reprint requests to: Miljenko V. Pilepich, M.D., Department of Radiation Oncology, Catherine McAuley Health Center, P.O. Box 995, Ann Arbor, MI 48106.

The end points of the study included an assessment of the effect of pelvic irradiation on disease-free survival, survival, and treatment-related morbidity.

RTOG-75-06.—From September 1976 to July 1983, 607 patients were accessioned to the study, and a total of 566 were analyzable. Of these, 500 had stage C, 63 stage B, and 3 stage A2 tumors. For the purposes of this and other RTOG studies, clinical stage is defined by the American Urological Staging System. Assignment of stage was based purely on clinical (physical) examination. Patients with evidence of nodal involvement were (for the purposes of this and other RTOG studies) designated as stages A, B, and C with lymph node involvement rather than stage D1.

RTOG 77-06.—From March 1978 to August 1983, 484 patients were entered on this study. Of the 444 who were considered analyzable, 360 had stage B and 84 had stage A2 disease.

REVIEW OF DATA ANALYSES

A series of analyses of RTOG 75-06 and 77-06 data has been undertaken since 1982 and will be reviewed here in some detail. Early analyses included only part of the study population.

Treatment-related Morbidity

All of the reported cases of treatment-related morbidity were recorded and classified with the use of the clinical severity grading schema shown in table 1. Commonly observed reactions to irradiation, such as diarrhea, were not registered as treatment-related morbidity (i.e., complications) unless they lasted beyond the first postirradiation month or unless they were grade 3 or higher. An attempt was made to separate various forms of treatment-related morbidity into specific disease entities and to define their incidence, the time of occurrence, and relation to treatment and their prognoses (1,2).

For the purposes of the study, a number of clinical syndromes, thought to represent specific types of normal tissue injury have been defined. For example, *cystitis* is defined as irritative bladder symptoms (dysuria, frequency) with or without hematuria. *Proctitis* is defined as irritative rectal symptoms characterized by tenesmus and/or mucus discharge with or without melena and with or without diarrhea. *Diarrhea* is characterized by loose, frequent bowel movements without irritative rectal symptoms. This syn-

TABLE 2.—Summary of treatment-related morbidity^a

Treatment-related morbidity	Grades					Total	
	1	2	3	4	5	No.	Percent
Cystitis	30	28	8			66	12.5
Diarrhea	20	30	1			51	9.7
Proctitis	14	20	6	1		41	7.8
Melena	14	6	2		1	23	4.4
Hematuria	4	4	8			16	3.0
Urethral stricture			12			12	2.3
Rectal-anal stricture	4	2	1			7	1.3
Vesical neck contracture			2	1		3	0.6
Rectal ulcer		1	2			3	0.6
Bowel obstruction				2		2	0.4

^a In studies RTOG 75-06 and 77-06, 526 patients received treatment.

drome is thought to result from the effect of irradiation on the segments of bowel proximal to the rectum. *Melena* is defined as any bleeding without associated proctitis symptoms.

A summary of treatment-related morbidity in 526 patients accessioned prior to 1981 is shown in table 2. It is apparent that an overwhelming majority of cases of treatment-related morbidity belong to grade category 1 and 2 and did not, by definition, affect the patient's performance status. Only a small proportion of cases (less than 1%) belong to grade category 4.

The pattern of occurrence varied considerably. Certain types of treatment-related morbidity occurred exclusively during the first year, whereas others showed an unpredictable pattern of occurrence (2).

Various types of complications also differed considerably as to their prognosis. In most cases, the symptomatology proved reversible. Figure 1 shows the pattern of resolution of proctitis. Over 70% of the patients who developed proctitis became asymptomatic by the end of the second year. A similar pattern of resolution was observed for diarrhea (fig. 2). The pattern of resolution of cystitis symptoms is shown in figure 3. Virtually all patients became asymptomatic by the end of the second year after occurrence.

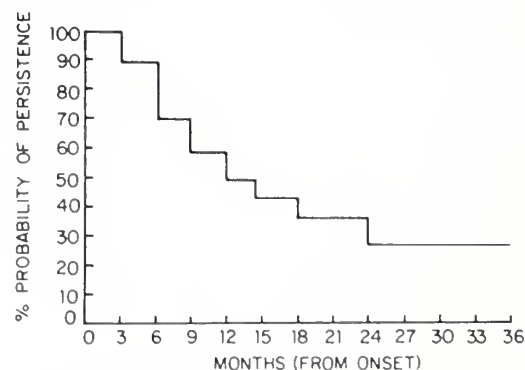


FIGURE 1.—Pattern of resolution of proctitis symptoms. All patients who developed proctitis at any time are plotted. Time of resolution is measured from onset of symptoms. Majority of patients with proctitis became asymptomatic within 2 yr after onset.

TABLE 1.—Grading of severity of complications

Grade	Complications
1	Minor symptoms requiring no treatment
2	Response to simple outpatient management, life-style (performance status) not affected
3	Distressing symptoms, altering of patient's life-style (performance status), possible hospitalization for diagnosis or minor surgical intervention (such as urethral dilatation) required
4	Major surgical intervention (such as laparotomy, colostomy, cystectomy) or prolonged hospitalization required
5	Fatal

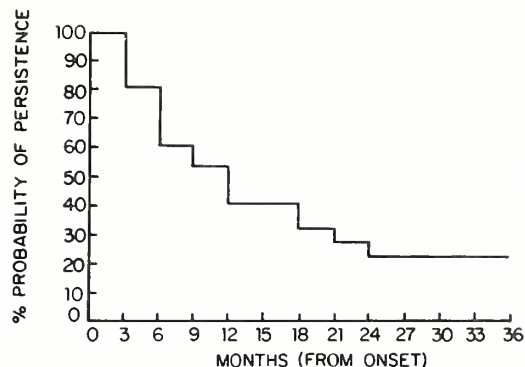


FIGURE 2.—Pattern of resolution of diarrhea. All patients who developed the symptoms at any time are plotted. Time of resolution is measured from onset of symptoms. Majority of patients with diarrhea became asymptomatic within 2 yr after onset.

The incidence of treatment-related morbidity was correlated extensively with a number of treatment parameters such as volumes, doses, and techniques (3,4). Extended fields were not associated with a significantly increased risk of complications. Periaortic irradiation compared with pelvic irradiation only was not associated with a significantly increased incidence of bowel injuries. Similarly, irradiation to the pelvis did not result in an increased risk of intestinal problems compared with irradiation to the prostate only.

A detailed correlation of the incidence and severity of treatment-related morbidity and total doses did not indicate a significantly increased incidence of bowel or bladder injuries within the range of doses delivered to the regional lymphatics.

The total doses to the prostate in excess of 7,000 cGy were not associated with a significantly increased incidence of bladder injuries but with an increased incidence of bowel injuries manifested by diarrhea and bleeding (fig. 4,5). Correlation with the treatment techniques revealed an increased incidence of bowel injuries in patients in whom pelvic irradiation consisted of parallel-opposed fields and also in those in whom prostatic boost consisted of opposed lateral fields or perineal fields (3,4).

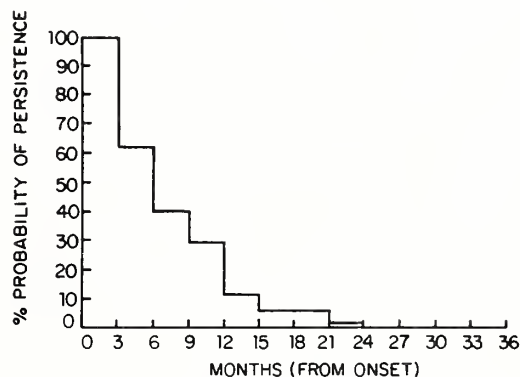


FIGURE 3.—Pattern of resolution of cystitis symptoms. All patients who developed symptoms of cystitis are plotted. Time of resolution is measured from onset. Virtually all patients became asymptomatic within 2 yr after onset.

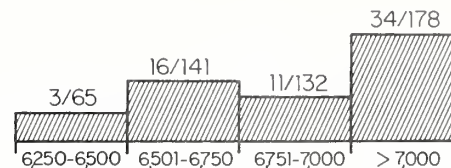


FIGURE 4.—Correlation of prostate (boost) dose and the incidence of diarrhea in RTOG 75-06. Figures above bars denote the number of cases of diarrhea per number of patients receiving the dose (6,250->7,000 cGy; $P < .01$ by Mantel-Haenszel test).

The analysis has shown that within the range of doses and treatment volumes used in the 2 studies, neither the volumes nor doses correlated well with the normal tissues effects. A dose-response for the bowel was evident only at doses above 7,000 cGy. It could be concluded that the choice of treatment volumes and doses (up to 7,000 cGy to the prostate) should be based primarily on the anticipated therapeutic effectiveness rather than the normal tissue considerations.

Treatment Arm Comparison

Analyses of the effect of the treatment arm assignment on the course of the disease in patients accessioned to study 75-06 showed no statistically significant difference between the treatment arms (5). Moreover, no significant difference between treatment arms could be documented within a number of subpopulations characterized by grade, hormonal status, stage, age, or acid phosphatase status. The results indicated no apparent benefit from elective periaortic irradiation in patients with detectable disease confined to the pelvis.

Analyses of treatment arm assignment in study 77-06 showed no statistically significant difference between treatment arms for the study population as a whole or within a number of subpopulations (Asbell SO, Krall JM, Pilepich MV, et al: Submitted for publication).

In summary, the treatment comparison analyses in both studies indicated that elective irradiation of regional lymphatics in carcinoma of the prostate may not be beneficial.

Analysis of Prognostic Factors

Extensive univariate and multivariate analyses of the factors of potential prognostic significance were also performed (6). These included tumor size, clinical stage, degree of histologic differentiation, nodal status, serum acid phosphatase status, hormonal management status, transurethral resection, and race. These factors were as-

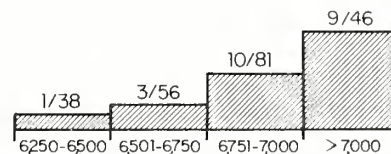


FIGURE 5.—Correlation of prostate (boost) dose and the incidence of rectal bleeding in RTOG 77-06. Figures above bar denote the number of cases of rectal bleeding per number of patients receiving the dose (6,250->7,000 cGy; $P < .01$ by Mantel-Haenszel test).

sessed as to their interdependence and correlation with the clinical course (study end points).

For the purposes of the study, tumor size is defined as a product of two perpendicular tumor dimensions in centimeters, as determined by physical examination on presentation.

Hormonal management status (either administration of estrogens and/or orchiectomy) was broken down into two categories dependent on the date of the initiation in reference to the first day of radiotherapy. If started within 60 days of the base date (first day of radiotherapy), the hormonal management was labeled as *concomitant*; otherwise, it was labeled as *antecedent*.

Univariate analysis identified the degree of histologic differentiation, age, and tumor size as factors of prognostic significance for local recurrence. Patients 60 years of age or younger were at a significantly higher risk of developing local recurrence. Patients with a tumor size characterized by a product of tumor dimensions of over 25 cm were also at a significantly higher risk of local recurrence (fig. 6).

The factors predictive of distant metastases included tumor size, histologic differentiation, serum acid phosphatase, and hormonal management status. Patients who received hormonal management prior to consideration of radiotherapy (antecedent hormonal management) exhibited a higher rate of distal metastases than those who had no hormonal manipulation and those who received hormonal manipulation in conjunction with radiotherapy (concomitant hormonal management). Populations receiving either antecedent or concomitant hormonal manipulation had a significantly higher proportion of cases with high-grade lesions, so that a higher rate of tumor progression could be anticipated. The observation that the incidence of distant metastases was the same in patients who received concomitant hormonal management as in those who did not may indicate a beneficial effect of endocrine manipulation when used as an adjuvant. This observation needs to be tested in a prospective study.

Elevation of serum acid phosphatase and larger tumor size were also associated with a high incidence of distal metastases.

Survival correlated well with the degree of histologic differentiation but did not correlate well with the serum acid phosphatase status and tumor size.

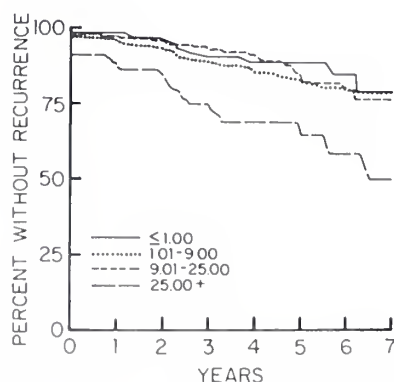


FIGURE 6.—Incidence of local-regional recurrence as a function of tumor size expressed as a product of tumor dimensions.

In the multivariate analyses of prognostic factors, use of a Cox regression model singled out the degree of histologic differentiation (expressed in the form of Gleason score) as the most important prognostic factor for all assessed end points. Tumor size and patient's age were also found predictive of local control. Serum acid phosphatase was found predictive of the incidence of distal metastases, but the degree of histologic differentiation proved to be the only factor predictive of survival.

A surprising observation was the lack of prognostic significance of nodal status in patients with clinical stage C disease. Although patients with positive nodes, proved by either lymphangiogram or lymphadenectomy, had a significantly higher proportion with high Gleason scores and elevation of serum acid phosphatase, their outcome proved comparable to those of patients with no evidence of nodal involvement and to those in whom the regional lymphatics were not evaluated (7). These findings may indicate that irradiation of the pelvis exerted a beneficial effect, possibly by curing a proportion of patients with limited nodal involvement. This hypothesis may need to be tested in a prospective study assessing the effect of lymphatic irradiation in patients with known involvement of regional lymphatics.

In contradistinction to the above observation, assessment of regional lymphatics in patients with primary tumor limited to the prostate (77-06 study population) proved valuable. It allowed identification of a subpopulation of patients who would ordinarily be considered candidates for radical prostatectomy and have an exceedingly good prognosis.

There were 104 such patients who had negative staging lymphadenectomy, detectable disease limited to the prostate, and normal serum acid phosphatase. With the median follow-up of 3 years and 9 months, only 5 patients developed evidence of distal metastasis (8). The disease-free survival and survival in this population compares favorably with the best of the surgical series. The observation indicates that the observed outcome in patients treated with definitive radiotherapy is at least equivalent, if not superior, to that in patients treated with radical prostatectomy.

CONCLUSIONS

Data accumulated in the 2 large-scale randomized phase III trials indicate that elective (prophylactic) irradiation of regional lymphatics in carcinoma of the prostate may not be beneficial. The term "elective" or "prophylactic irradiation" refers to irradiation of the periaortic area in patients with locally advanced disease confined to the pelvis and to pelvic irradiation in patients with known disease confined to the prostate. The studies were not designed to test the value of therapeutic irradiation, i.e., irradiation of the involved lymphatics. Each patient with known involvement of the pelvic lymphatics received pelvic irradiation.

The outcome in patients with clinical stage C disease and involvement of pelvic regional lymphatics proved comparable to that in node-negative patients. This observation may indicate a beneficial effect of therapeutic lymphatic irradiation. This contention must be tested in a prospective trial.

Irradiation of the regional lymphatics does not result in a significantly increased incidence of treatment-related morbidity compared with prostate irradiation only.

The treatment-related morbidity has been qualified and quantified in great detail. The incidence of serious treatment-related complications proved to be low. Most of the treatment-related symptomatology proved reversible. Within the range of doses used in the RTOG studies, no dose-response could be identified for doses ranging from 6,500 to 7,000 cGy. Doses in excess of 7,000 cGy seem to be associated with an increased risk of bowel morbidity.

Local-regional control is satisfactory in the limited size primaries. Novel approaches are necessary in patients with bulky primaries.

In populations characterized with disease clinically limited to the capsule and negative lymphadenectomy, the outcome appears at least comparable, if not superior, to that in surgically treated patients.

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Radiation Therapy for Localized Prostate Carcinoma: Experience at the Massachusetts General Hospital (1973-1981)

W. U. Shipley,* G. R. Prout, Jr., N. M. Coachman, P. L. McManus, E. A. Healey, A. F. Althausen, N. M. Heney, E. C. Parkhurst, H. H. Young II, J. W. Shipley, S. D. Kaufman^{1,2}

ABSTRACT—The success following irradiation in 370 patients with clinically localized prostate carcinoma was measured by overall patient survival as well as the cumulative incidence with time of treated patients who developed either local tumor regrowth or progression with distant metastases. With a minimum follow-up of 5 years in living patients, we evaluated the cumulative frequency curves using both univariate and multivariate (Cox) analyses. Overall patient survival and probability of progression with distant metastases were significantly influenced by initial tumor stage and the degree of histologic differentiation. The results at 8 years are significantly better for patients with T2 (B) tumors (local regrowth in 8%, distant metastases in 18%) than for patients with T3-T4 (C) tumors (local regrowth in 28%, distant metastases in 60%). Patient tolerance of external-beam radiation therapy was carefully analyzed in 121 consecutively treated patients in 1980 and 1981 for subsequent radiation-related sequelae. Minor transient intestinal and urologic sequelae were observed in 21% and 23% of the patients, respectively. These mild to moderate symptoms resolved in all but 7% of the patients who are continuing with mild symptoms. One patient had a major complication, i.e., a cystectomy required for persistent bleeding. Erectile potency has been maintained in 63% of potent patients. No specific benefit or detriment in outcome was seen in the minority of 51 patients who were irradiated by iodine-125 implantation. We conclude from these results that, for patients with stage T2 tumors, the results with radiation therapy and surgery are good and are similar for at least 8-10 years of follow-up; thus patients should decide which treatment they would prefer after being fully informed. For patients with T3 and T4 tumors, the results are significantly poorer than for those with T2 tumors. Rigorous clinical research will be necessary in patients with T3 and T4 tumors to document possible benefit from either more aggressive local treatment or from adjuvant systemic therapy (such as androgen deprivation) against the undetected distant metastases, which are the major clinical problem for men with tumors of this stage.—NCI Monogr 7:67-73, 1988.

The success following local treatment (by either irradiation or surgery) for patients with clinically localized prostate carcinoma may be evaluated by several methods.

These include overall survival, survival without evidence of tumor progression, or by separate evaluation of the curves of the cumulative incidence with time of treated patients who developed either local regrowth or distant metastasis. We have used the latter approach to evaluate the clinical patterns of failure following radiation therapy for patients with localized prostate carcinoma. For an analysis of the incidence of either local regrowth or the development of distant metastases, the assessment depends on both the duration of the observation period and the physician's ability to discriminate clinically between local regrowth and other local changes, as well as between distant metastases and other abnormalities. The prognostic factors of tumor grade and clinical stage have been reported in many surgery and radiation therapy series to influence significantly overall survival and progression to distant metastasis (1-10). However, few investigators have evaluated additional prognostic factors by multivariate analysis. This present retrospective analysis is of survival and of the cumulative frequency of the development of local tumor regrowth and of distant metastases observed in 370 patients irradiated at this institution for prostate cancer. The possible independent and significant prognostic influence of six tumor and patient characteristics was evaluated by multivariate analysis. Observation periods range from 5 to 12 years.

PATIENTS AND METHODS

This retrospective analysis is on all 370 patients irradiated at the Massachusetts General Hospital Cancer Center from 1973 to 1981 for clinically localized and palpable carcinoma of the prostate. We have grouped our patients into the 1983 American Joint Committee TNM Staging System (11). All patients at diagnosis were stage M0. One hundred thirty-five, or 36%, of the patients in this series underwent a pretreatment staging lymphadenectomy, and thus the majority (235 of 370) at diagnosis were stage NX. The radiation therapeutic techniques have been described (6,12,13) for both the group of 319 patients treated by external-beam radiation therapy as well as the 51 patients who were treated by low-dose, preoperative external-beam radiation therapy and retropubic iodine-125 interstitial implantation. Conventional external-beam irradiation to the true pelvic lymph nodes (5,040 cGy) by a contoured four-field box technique was followed by a boost to the primary tumor volume, from 6,400 to 7,000 cGy, in 259 patients with photon beams of 10-42 megavolts. Sixty additional patients had the boost to the prostatic tumor volume by the perineal portal with 160-million electron volt protons to total doses up to 7,700 cobalt cGy equivalents (12). Another 51

¹ Radiation Medicine Service (W. U. Shipley, N. M. Coachman, P. L. McManus, E. A. Healey, J. W. Shipley), Urologic Surgery Service (G. R. Prout, Jr., A. F. Althausen, N. M. Heney, E. C. Parkhurst, H. H. Young II), and Medical Oncology Service (S. D. Kaufman), Massachusetts General Hospital Cancer Center, Boston, MA.

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* Reprint requests to: William U. Shipley, M.D., Radiation Medicine Service, Massachusetts General Hospital Cancer Center, Cox Bldg. 3, Boston, MA 02114.

TABLE 1.—American Joint Committee TNM Staging System, 1983

Stage	Definition ^a	Comment
T1	No palpable tumor; T1a: no more than 3 high-power fields of carcinoma found on histologic sections; T1b: more than 3 high-power fields of carcinoma found on histologic sections	
T2	Palpable tumor limited to (within) the prostatic capsule	
T2a	Palpable tumor occupying <50% of one lobe and < 1.5 cm in diameter	Same as, or nearly identical to, what has been reported as stage B1 by the Memorial system or as stage T1a and T1b by the Stanford system
T2b	Palpable tumor occupying > 50% of one lobe, > 1.5 cm in diameter, and/or more than one lobe or containing more than one nodule	Same as, or nearly identical to, what has been reported as stage B2 by the Memorial system or as stage T1c and T2 by the Stanford system
T3	Palpable tumor extending into and usually beyond the prostatic capsule	Same as stage C in the Memorial system and stage T3 in the Stanford system
T4	Palpable tumors with attachment to the pelvic side walls or with invasion of the rectal wall or bladder	Same as stage D1 in the Memorial system and as stage T4 in the Stanford system

^a See (11).

patients were treated by 1,050 cGy as preoperative radiation therapy and an iodine-125 interstitial implantation of 16,000 cGy, total decay (13). Patients with stage T1 (A) tumors were omitted from this analysis because in patients with a palpable tumor, we wished to evaluate the possible significance of symptomatic bladder outlet obstruction requiring a transurethral resection on local regrowth or distant metastases. Because, by definition, all stage T1 patients would have had a transurethral resection and no palpable tumor, their inclusion for this prognostic variable was not appropriate.

The follow-up has been done by the radiotherapist and the referring urologist. The response of the primary tumor is based on the serial digital rectal examination as well as on the urologic evaluation, when clinically indicated, of bladder outlet or ureteric obstruction or of pain as a possible result of local tumor regrowth. The development of distant metastases, which occurred in 99 of 370 patients, was usually diagnosed by development of a positive bone scan, of abdominal lymph nodal metastases diagnosed by computed tomography or, rarely, development of pulmonary or hepatic metastases. Routine interval bone scans were not done on asymptomatic patients. These examinations were done only for symptomatic patients or for those asymptomatic patients on whom rising serum acid phosphatase levels were detected. Hormonal and radiation therapy were used simultaneously in 77 of the 370 patients. Hormonal therapy was routinely reserved for those patients with evidence of tumor progression. The six tumor and patient factors evaluated in this report include: primary tumor stage (table 1), degree of tumor differentiation (well and moderately well vs. poor), age at diagnosis (\geq the population mean of 67.8 yr), the method of diagnosis (needle biopsy vs. transurethral resection), and stable or elevated serum acid phosphatase levels at the time of diagnosis. Whether initial hormonal therapy (diethylstilbestrol or bilateral orchiectomy) was used did not influence the evaluation.

The actuarial tumor regrowth or recurrence time distribution curves were calculated by the Kaplan-Meier life table method, and the tests for differences in the curves were by log rank. We assessed the relative prognostic signifi-

cance of the six patient and treatment variables using the Cox proportional hazard model (14).

RESULTS

Overall Patient Survival

The overall survival by actuarial calculation for patients grouped by clinical stage is shown in figure 1, with a statistically significant difference by univariate analysis of P less than .0001 and by multivariate analysis of $P = .0013$ (table 2). The only other prognostic factor significantly and independently influencing overall survival was degree of tumor differentiation ($P = .0059$; table 2). This influence of degree of differentiation is shown for the stage T2 patients in figure 2. Figure 3 illustrates that the overall survival for T2 patients treated either by external-beam radiation therapy or by retropubic iodine-125 interstitial implant was similar. Having symptomatic bladder outlet obstruction that required a transurethral resection at the time of

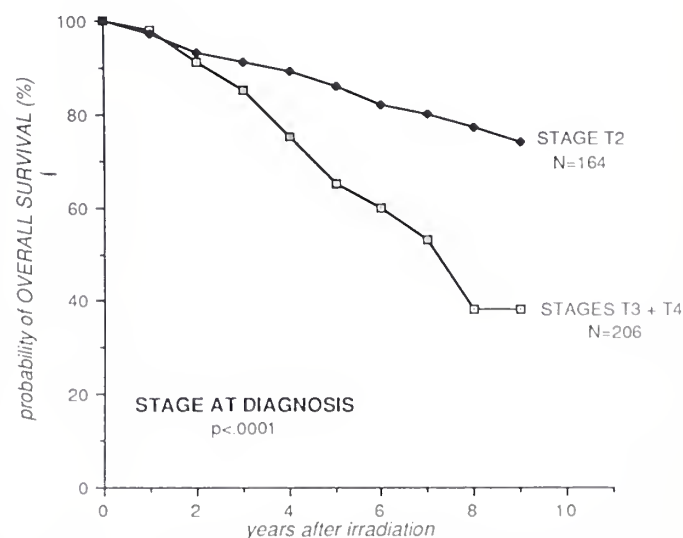


FIGURE 1.—Overall survival of 370 irradiated patients with tumors subgrouped by stage (T2 vs. T3-T4).

TABLE 2.—Overall survival

Variable	Regression coefficient	P
Tumor stage	3.22	.0013
Histologic differentiation	2.75	.0059
Transurethral resection of the prostate	1.89	.06
Initial hormonal therapy	0.68	.49
Elevated serum acid phosphatase	-0.43	.67
Age at diagnosis	-0.28	.77

diagnosis was an unfavorable prognostic sign of borderline significance ($P = .06$; table 2).

Local Tumor Regrowth

The stage (local tumor extent and/or invasiveness) was the one and only significant prognostic factor of local tumor regrowth in this series (see fig. 4 and table 3). However, its influence was highly significant ($P = .0006$) and showed a 28% incidence of local recurrence by 8 years in those patients with stages T3 and T4 tumors, as compared with only 8% for patients with clinical stage T2 tumors. The differences in the length of posttreatment observation time among any 2 groups being compared makes either the development of local tumor regrowth or the development of distant metastases better evaluated by the cumulative frequency method (i.e., actuarial recurrence time distribution curve) rather than the proportion of patients developing either local regrowth or distant metastases. For instance, in figure 4, the cumulative frequency of local tumor regrowth at 8 years is 28% in the patients with T3 and T4 tumors, whereas the proportion of T3 and T4 patients who have developed a local regrowth (34 of 206 or 17%) is much lower.

The curve over time for patients with T2 tumors may be nearly flat beyond 5 years, but the curve for stage T3-T4 patients is continuing to increase up to and probably beyond 8 years of observation. The cumulative frequency of local regrowth is similar in stage T2 patients, whether the treatment is by external-beam irradiation or by iodine-125 implantation (fig. 5). In addition, the cumulative frequency

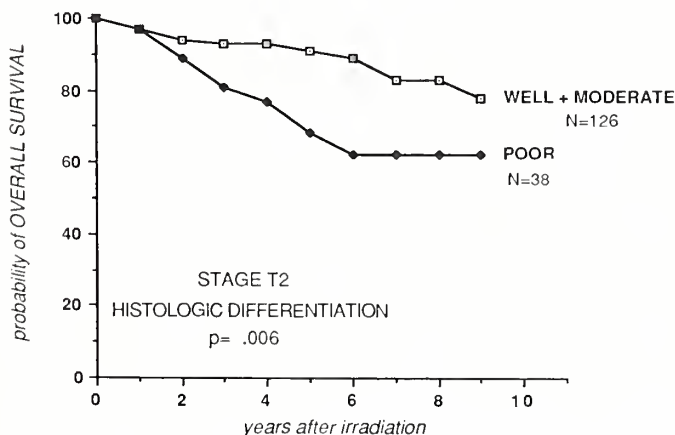


FIGURE 2.—Overall survival for stage T2 patients subgrouped by histologic differentiation (well and moderate vs. poor).

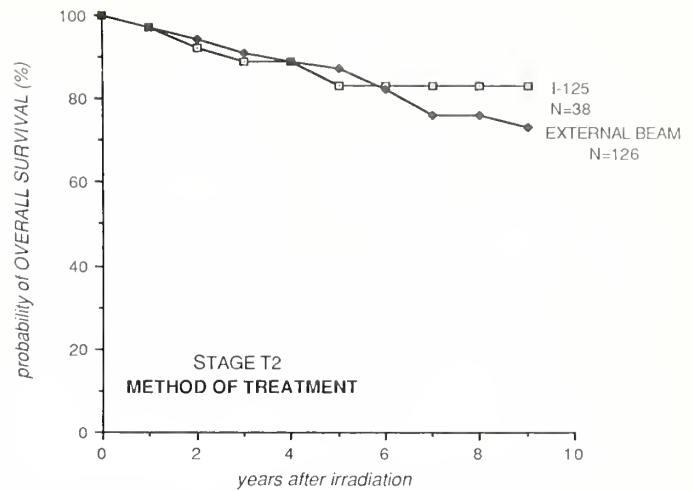


FIGURE 3.—Overall survival of stage T2 patients treated either by external-beam irradiation or by interstitial iodine-125 implantation.

of patients developing local tumor regrowth for those with specified initial tumor stage is not influenced by previous initial hormonal therapy or lack of it (fig. 6).

Development of Distant Metastases

The cumulative incidence of progression with distant metastases is also significantly influenced by initial tumor stage ($P = .00007$ by multivariate analysis). Within tumor stage (T2 vs. T3 or T4), histologic differentiation (well or moderate vs. poor) is a statistically significant variable predicting progression to distant metastases (fig. 7). Only 16 of the 164 stage T2 patients had elevated acid phosphatase levels at diagnosis. By univariate analysis, an increase in the cumulative incidence of progressing with distant metastases at the $P = .05$ level was predicted. However, elevated acid phosphatase at diagnosis “co-varied” with poor differentiation, such that it was of no independent statistical significance by multivariate analysis.

One hundred thirty-five of the patients in this series had surgical staging of their lymph nodes prior to irradiation.

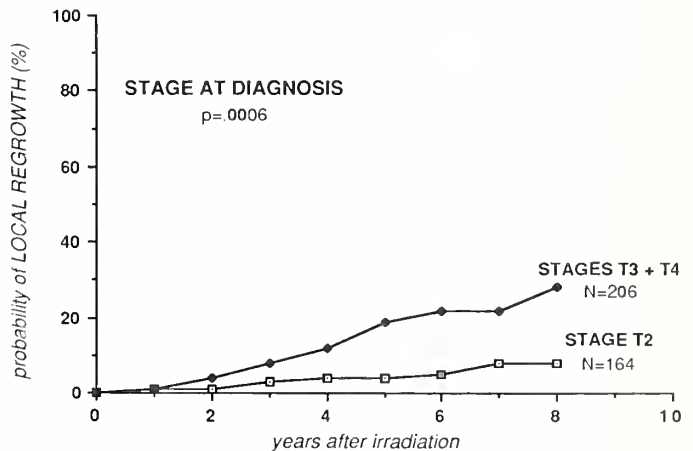


FIGURE 4.—Cumulative incidence (actuarial time distribution curve) of local regrowth of tumor subgrouped by clinical stage (T2 vs. T3 and T4).

TABLE 3.—Local regrowth^a

Variable	Regression coefficient	P
Tumor stage	3.41	.0006
Elevated acid phosphatase	-0.85	.39
Transurethral resection of the prostate	0.77	.44
Age at diagnosis	-0.69	.49
Histologic differentiation	0.51	.61
Initial hormonal therapy	-0.25	.80

^a Data for 370 patients were evaluated by multivariate analysis.

For stage T2 patients, microscopic lymph nodal status was a significant predictor of progression to distant metastases ($P = .02$; fig. 8) but was not significant in the 72 patients undergoing such evaluation who were stage T3 and T4 (fig. 9).

Radiation Sequelae Following High-energy, Photon-beam Irradiation

Both the acute and late radiation reactions in patients treated by iodine-125 implantation (13) and by perineal proton boost irradiation (6) have recently been reported. The present analysis is on 121 patients treated on a linear accelerator with a photon beam of 25-megavolt peak energy. These patients were treated from January 1980 through December 1981. We treated all with 180-cGy fractions, 5 sessions per week using the previously described four-contoured field box technique to include the primary tumor volume and the pelvic lymph nodes below the bifurcation of the common iliacs to a dose of 5,040 cGy in 28 fractions. The prostatic tumor volume was then treated by a cone-down boost with contoured parallel-opposed lateral fields to a total tumor dose of 6,480 cGy to 6,840 cGy in 180-cGy fractions, 5 sessions per week.

The genitourinary radiation sequelae are shown in tables 4-6. Only 1 of 121 patients (i.e., 0.8%) sustained a major complication, which was a radical cystectomy for persistent bleeding in a patient with an original stage T3 tumor who

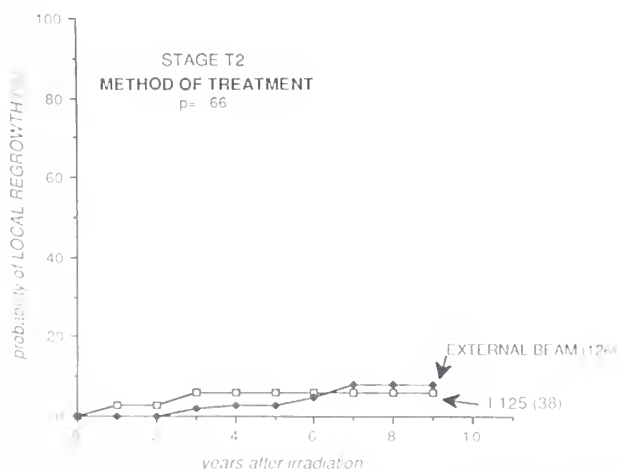


FIGURE 5.—Cumulative incidence of local tumor regrowth for patients with stage T2 tumors treated either by external-beam irradiation or iodine-125 implantation.

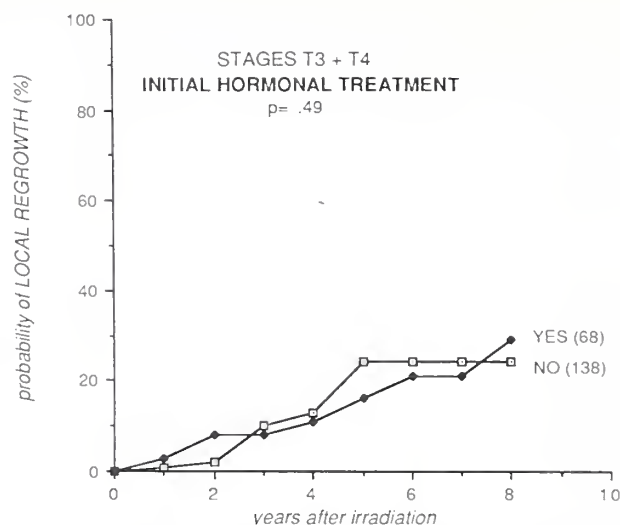


FIGURE 6.—Cumulative incidence of local tumor regrowth for patients with stage T3 and T4 tumors subgrouped by treatment with initial hormonal therapy plus radiation or no treatment, or by radiation therapy alone.

had no microscopic cancer residual in his prostate, but had a preexisting thrombocytopenia due to hypersplenism. No patient is incontinent (table 4). Of the 10 urethral strictures or bladder neck contractures seen, all were observed in the first 2 years following irradiation (table 5), and 9 were readily corrected by transurethral surgery. One patient still has moderately severe urinary frequency but is continent. The overall incidence of stricture or bladder neck contracture was 8.3% (10 of 121). However, the incidence was 14% (9 of 63) in those patients who had undergone a transurethral resection prior to radiation therapy. By contrast, there was a significantly lower incidence of stricture (1.7% or 1 of 58) in those patients not having to undergo transurethral prostatic resection prior to radiation therapy. Erectile potency for 3 or more years has been maintained in 34, for an incidence of 63% (table 6). At diagnosis, erectile potency was

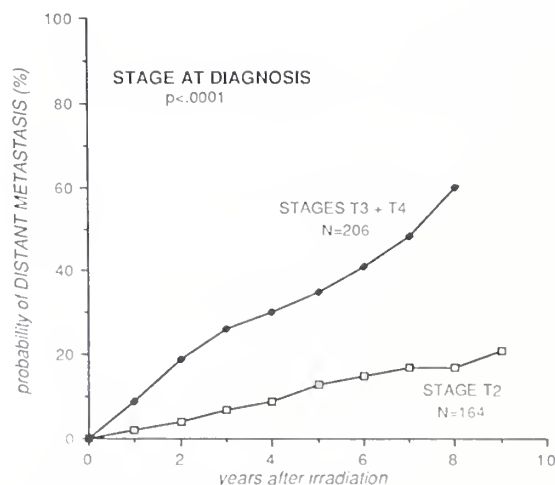


FIGURE 7.—Cumulative incidence of progression with distant metastases for all irradiated patients with tumors subgrouped by stage (T2 vs. T3 and T4).

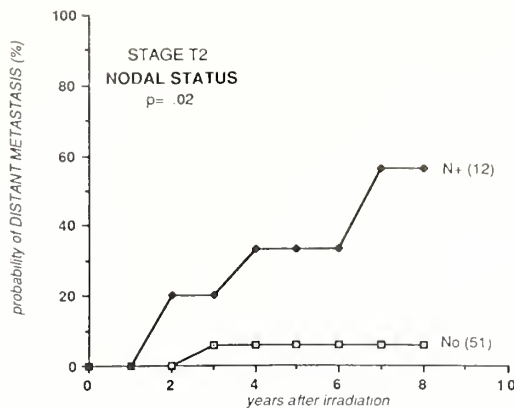


FIGURE 8.—Cumulative incidence of progression with distant metastases for patients with stage T2 tumors subgrouped by histologic evaluation of lymph nodal status subsequent to staging pelvic lymphadenectomy.

present in 54 of the irradiated patients. The initial tumor stage did not influence the incidence with which potency was maintained.

The Radiation Therapy Oncology Group grading system was used for the radiation sequelae shown in table 7. Diarrhea persisting 3 or 4 months following radiation therapy or rectal bleeding that did not require any medication (patient's wish) occurred in 12%, although in an additional 9% of the patients, these symptoms were judged "moderate" because the patient wished to use a medication (either an antispasmodic agent or an anal suppository). These mild to moderate radiation sequelae have been resolved in all but 8 patients; 4 have persistent but controlled (with medication) diarrhea, and 4 have infrequent mild episodes of hemorrhoid-like rectal spotting with blood. No patient has required surgery for any intestinal complication. Within the diarrhea subcategory, 11 of 15 patients have had their symptoms resolved and, among the 22 patients with infrequent rectal bleeding, 18 have had this symptom completely resolved.

Thus radiation sequelae that have persisted are infrequent (table 8). Minor rectosigmoid irritation symptoms persist

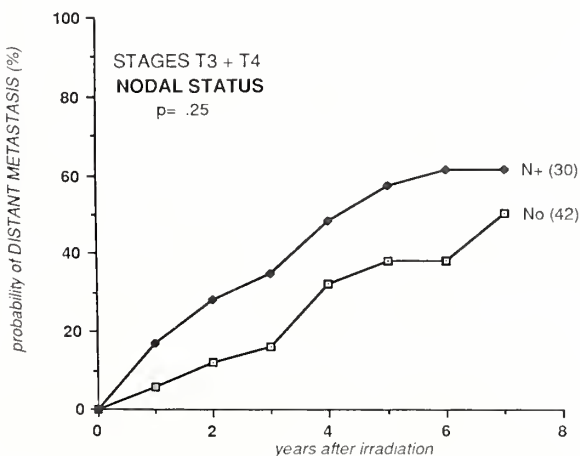


FIGURE 9.—Cumulative incidence of progression with distant metastases for patients with stage T3 and T4 tumors subgrouped by histologic evaluation of lymph nodal status subsequent to staging pelvic lymphadenectomy.

TABLE 4.—Genitourinary radiation sequelae

Sequelae	Incidence in 121 patients	
	No.	Percent
Hematuria	21	17.0
Resolved	20	95.0
Persistent	1	0.8
Incontinence	0	0

in 6.6% of the patients. Minor urologic symptoms persist in 0.8% of them, and a major complication occurred and was surgically corrected by cystectomy in 0.8%. There have been no major sequelae in the small intestine. Erectile impotence has occurred in 37% of previously potent patients. Two patients underwent an uneventful hip replacement for progressive degenerative joint disease, although it is not likely that development of this disease was influenced, for better or worse, by the radiation (4,500 cGy to the femoral heads) that all 121 patients received.

DISCUSSION

Many observations in this single-institution, retrospective analysis are similar to those reported (1-10). This is especially true for the prognostic influence of the primary tumor size as well as the degree of histologic differentiation on the subsequent development of disease progression and on overall patient survival. Most of these reports, including the present one, tell of a follow-up that is very limited beyond 10 years from treatment. However, the results from studies by researchers at Stanford University Medical Center have follow-up after radiotherapy for up to 27 years (5,15), and those at the M. D. Anderson Hospital and Tumor Institute have 77 patients who have been evaluated for more than 10 years after treatment (16). A histologic sampling by either transurethral resection or Silverman needle biopsy may undergrade the primary tumor relative to the findings at radical prostatectomy in 25% to 33% of the patients (17,18). However, the consistent and statistically very significant influence that poorly differentiated tumor has on treatment outcome in virtually all the reported series suggests the important usefulness of the clinical grade of the tumor.

Our results give additional documentation to the importance of primary tumor size as influencing the subsequent probability of patients developing either a local tumor regrowth or progression with distant metastases. For the stage

TABLE 5.—Genitourinary radiation sequelae

Sequelae	Incidence in 121 patients	
	No.	Percent
Stricture	10	8.3
Prior transurethral resection of the prostate	9/63	14.0
No prior transurethral resection of the prostate	1/58	1.7
Corrected strictures	9	90
Persisting symptoms	1	0.8

TABLE 6.—Genitourinary radiation sequelae

Sequelae	No.	Percent
Potent prior to radiation therapy	54/121	45
Potency maintained	34	63
Stages T1-T2	22/39	56
Stages T3-T4	12/15	80

T2 (B) tumors, the local control rate is 92%, compared with only 72% at 8 years for those with stages T3 and T4 (C) tumors. Likewise, initial tumor size was highly significant with regard to the probability of patients developing progression with distant metastases; e.g., at 8 years, this was 18% for patients with stage T2 tumors and 60% for those with stage T3 or T4 tumors. In all multivariate analyses, no single factor was more significant than initial tumor stage, including when such an analysis was done on the subgroup of 135 patients who had surgical staging of the pelvic lymph nodes. The implications of these observations are that earlier diagnosis, improvements in the local treatment of subgroups of patients with T3-T4 tumors, and development of some effective, tolerable, systemic, cytotoxic treatment will be of enormous benefit.

Our frequency of local regrowth agrees quite well with most other series. For instance, our permanent local tumor control rate for patients with stage T2 (B) tumors is similar to that following radical prostatectomy reported by Gibbons et al. (19). They report local tumor regrowth in 6% of 195 stage B patients with from 4 to 30 years of observation, although they do not use the actuarial technique of calculation, and some of those patients received postprostatectomy irradiation. Most radiation therapy series use actuarial calculations and have similar results. However, this is not true for the series from the Baylor College of Medicine, in which a combination of external-beam irradiation and radioactive gold-198 interstitial brachytherapy was used (20). In 124 patients ranging in stage from A2 to C1, the actuarial local recurrence rate at 10 years was 49%. This rate contrasts sharply with the actuarial 10-year local recurrence rates from other radiation series, i.e., at Stanford University Medical Center, this recurrence rate was 21% in 799 patients with stages B and C tumors (15); at the M. D.

TABLE 7.—Late bowel radiation sequelae^a

Grade ^b	Sequelae Manifestation	Incidence in 121 patients		Persisting symptoms	
		No.	Percent	No.	Percent
1	Mild diarrhea or bleeding (no medication required)	14 ^a	12	5	4
2	Moderate diarrhea or bleeding (treated with medication)	12 ^a	10	3	2
3	Surgery for bleeding	0	0	0	0
4	Surgery for fistula or obstruction	0	0	0	0
5	Death	0	0	0	0

^a Sequelae were resolved in 69% of patients (18 of 26).

^b The Radiation Therapy Oncology Group grading system was used.

TABLE 8.—Persistent radiation sequelae

Symptoms	Percent
Urologic	
Minor	0.8
Major	0.8
Rectal	
Minor	6.6
Major	0.0
Erectile impotence	37.0

Anderson Hospital and Tumor Institute, this rate was 19% for 551 stage C patients (16), and here at Massachusetts General Hospital, we reported a recurrence rate of 22% for 370 stage T2-T4 (B-C) patients. This lower recurrence frequency was also seen in patients who did not receive initial hormonal therapy (fig. 6, table 3). The reason for the high regrowth rates following gold-198 brachytherapy combined with external-beam irradiation may be related to radiation dose inhomogeneity because a significant proportion of the prostate received no more than 5,000 cGy (21). The correlation shown in the Baylor series between a positive postirradiation biopsy and the development of distant metastases most likely results because both are known to be strongly influenced by initial tumor volume (20). In small tumors, the incidence of progression with distant metastasis is low as is the incidence of positive tumor biopsy postirradiation. In larger tumors both incidences are high. Only when a large series of patients with similarly sized tumors are analyzed for the relationship between positive tumor biopsy following irradiation and progression with distant metastasis could a causal relationship be suggested.

For patients with tumors of comparable stage, e.g., T2a or the B1 nodular tumors, the 15-year overall survival following either radical prostatectomy (19,22,23) or radiation therapy (4) is similar and ranges from 51% to 57%. Although some differences in patient selection may exist in these series, the overall local efficacy of either radiation therapy or surgery is high and similar. Therefore, we judge that the patients with stage T2 (B) tumors should decide which treatment they prefer after being fully informed as to available therapy and the possible sequelae. For patients with the larger stage T3-T4 tumors, we believe rigorous clinical research is necessary in any attempt to document techniques of improved therapeutic efficacy. At present, we are running a randomized phase III trial for patients with T3-T4 tumors of conventional 25-megavolt photon therapy to doses in the conventional dose range of 6,800 cGy, compared with the perineal proton boost allowing the tumor volume to be raised safely to exposure to a total dose of 7,600 cGy. We believe that undetected distant metastases are the major clinical problem in patients with locally advanced prostate adenocarcinoma and await the development of effective and tolerable adjuvant systemic therapies.

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External-beam Radiation Therapy for Clinically Localized Prostate Cancer: Patterns of Care Studies in the United States

Gerald E. Hanks¹

ABSTRACT—Data are presented from the Patterns of Care Study and other sources that define the role of external-beam irradiation in the management of localized prostate cancer as practiced in the United States as a whole. Patients must be treated with complex treatment techniques and high-energy linear accelerators and careful adjustment of radiation dose. Transurethral resection of the prostate should be avoided in the intermediate and poorly differentiated subgroup of stage C patients. The excellent 5- and 10-year survival for patients treated by radiation therapy is demonstrated for all stages of prostate cancer and for T1 or early stage B patients. It is noted that the national averages for survival have improved between 1973 and 1978. Stages A2 and B patients with negative lymph node dissections show freedom from recurrence that is equal to patient reports for radical surgery. Complications resulting from radiation therapy were modest, and potency was maintained in 73% of the patients. Adjuvant irradiation is necessary for pathologic stage C patients after recovery from surgery. Radiation therapy is equally effective though less costly than surgery for early prostate cancer. A particular need of future research is the study of the patterns of care in the United States regarding the surgical management of prostate cancer so that health professionals can determine if this care is generally available throughout the United States and if good outcome and acceptable morbidity result after it is given.—NCI Monogr 7:75–84, 1988.

These data were collected for this National Consensus Panel to help answer the following questions:

- What methods are optimal for definitive radiation therapy?
- What are the long-term results in control and survival?
- What is the morbidity of the procedures?
- How can it be minimized?
- Should definitive radiation therapy be used as an adjuvant in high-risk patients?
- What directions for future research are indicated?
- When is pelvic node dissection necessary and who are the candidates?

In addition, some unique data will be presented on the relative costs of the alternative forms of management of early prostate cancer.

PATIENTS AND METHODS

Data are presented from the Patterns of Care Study in Radiation Therapy, the author's former practice in Sacramento, California, and from the literature.

ABBREVIATION: TURP = transurethral resection of the prostate.

¹ Department of Radiation Therapy, Fox Chase Cancer Center, Central and Shelmire Ave., Philadelphia, PA 19111.

The Patterns of Care Study technology has been reported (1–3). Suffice to say that this two-level random sample of the practice in the United States represents true national averages for 2 surveys of patients who were treated either in 1973 and 1974 or in 1978 (4). A third survey was conducted on patients treated in 1973 in the five facilities in the United States where the largest numbers of patients with prostate cancer were treated. These special data are added to those of the 2 previous surveys only for the determination of dose-response relationships for infield control. A summary of patient records that were reviewed is shown in table 1.

The information presented concerning the relative cost of radiation therapy and surgery was gathered by an assessment of the average cost of 1) treatment with external-beam irradiation for 128 patients, 2) radical prostatectomy for 12, and 3) ¹²⁵I seed implantation for 8 patients undergoing lymph node dissection in Sacramento, California, during 1984 (5). The costs of each method of treatment were determined from the point of our having obtained a positive biopsy and a negative metastatic workup. They include all technical, professional, and hospital inpatient and outpatient charges and are accurate for the private practice of radiation therapy and urologic surgery at the time and site studied.

Staging is by the A, B, C system common to practice in the United States (6).

RESULTS

Need for Complex Technology

Table 2 illustrates the reduction in complications observed when patients are treated with multiple field techniques or multiple fields per day (7,8). An advantage in any recurrence and in infield recurrence when linear accelerators are used with energies of 6 million electron volts or greater as contrasted to 4-million electron volt linear accelerators or cobalt-60 units is shown in table 3 (9).

Importance of Dose Selection and Method of Diagnosis

Tables 4–6 depict dose-response relationships for infield failure in 1,516 patients (10). Looking at all the patients, one would conclude that the range of 6,500 to 7,000 cGy is appropriate. When one considers individual stages, there is no advantage to exceeding 7,000 cGy for stage B cancer, although for stage C there is a decrease in local failure when the maximal dose to the center of the prostate is 7,000 cGy or greater. Thus dose must be adjusted to tumor volume (4). These same investigators have observed a doubling of complications from 3.5% to 6.9% ($P = .03$) when dose exceeds 7,000 cGy, which emphasizes that these high doses should be restricted to patients with extensive local disease (4,7,10). In

TABLE 1.—Patterns of Care Study data base

Survey sample	Years of treatment	No. of patient records reviewed	Stage		
			A	B	C
National average	1973, 1974	674	66	312	296
Special purpose	1973	188	5	62	121
National average	1978	733	115	381	237

TABLE 2.—Patterns of Care Study

Radiation therapy	No. of patients	Complication, %
Technique		
Anterior/posterior-posterior/anterior	301	6.0
Other	328	3.0
Fields/day		
1	187	6.0
2-6	426	3.5

TABLE 3.—Correlation of photon energy with recurrence

Treatment source ^a	Total No. of patients	Percent recurrence	
		Any ^b	Locoregional ^c
Cobalt-60	309	33	20
6 MeV	305	31	18
6-8 MeV	108	19	10
20 MeV	138	24	10

^a MeV = million electron volts.^b $P = .02$.^c $P \leq .01$.

TABLE 4.—Patterns of Care Study: Relationship of dose to infield recurrence, all stages, 1,516 patients

Dose, cGy	No. of infield failures/total	Percent	Percent actuarial free of recurrence ^a	
			5 yr	7 yr
<6,000	41/178	23	71	62
6,000-6,499	51/269	19	76	73
6,500-6,999	85/548	16	83	79
7,000+	74/521	14	84	79

^a By linear trend $P = .0001$; Mantel $P = .0009$.

TABLE 5.—Patterns of Care Study: Relationship of dose to infield recurrence in 724 stage B patients

Dose, cGy	No. of infield failures/total	Percent	Percent actuarial free of local recurrence ^a		
			3 yr	5 yr	7 yr
<6,000	22/87	25	85	71	—
6,000-6,499	16/120	13	94	82	77
6,500-6,999	37/283	13	91	88	77
7,000+	32/234	14	93	84	78

^a For unstratified, linear trend, $P = .0021$ and Mantel, $P = .0203$.

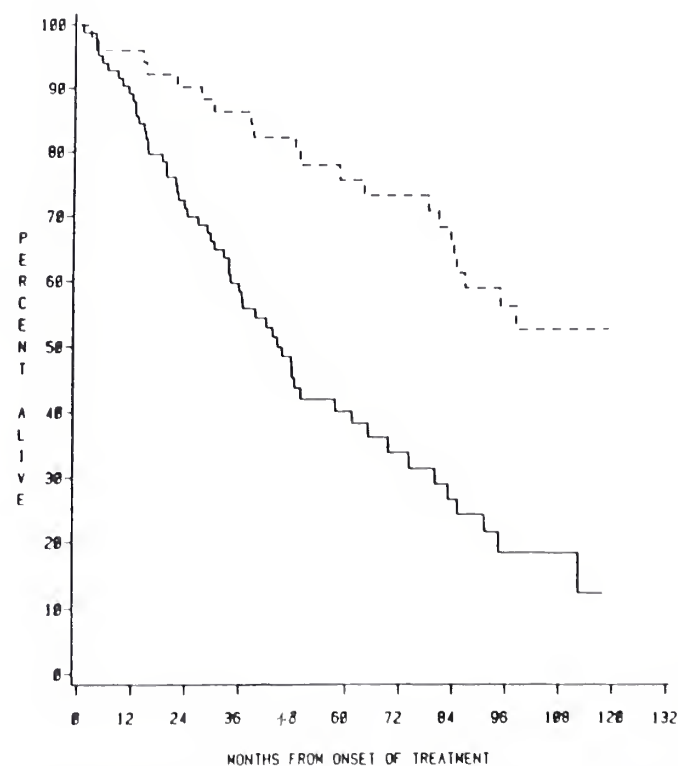
TABLE 6.—Patterns of Care Study: Relationship of dose to infield recurrence in 624 stage C patients

Dose, cGy	No. of infield failures/total	Percent	Percent actuarial free of recurrence ^a		
			3 yr	5 yr	7 yr
<6,000	17/69	25	72	63	—
6,000-6,499	31/111	28	76	64	64
6,500-6,999	46/200	23	83	72	68
7,000+	42/244	17	86	81	76

^a For unstratified, linear trend, $P = .0021$ and Mantel, $P = .0203$.

addition, we could calculate that there would have been an 8% improvement in local control and a 10% improvement in complications if optimal doses were administered to patients in each stage who were treated in 1973 and 1974 (4).

Patients with intermediate and poorly differentiated stage C cancer who undergo TURP as a method of diagnosis have a poor prognosis as illustrated by figures 1-3 (4,11,12), whereas no adverse effects have been observed in those with well-differentiated cancers. Significant increases are observed in both metastasis and death. How the subset of patients is affected is shown in table 7. Possible mechanisms include: The cancer is disseminated by the procedure or, in some indirect way, obstruction helps to select a poor prognosis subgroup separate from known prognostic indicators (4). Investigators (13-15) who reported no effect from TURP may not have looked at the appropriate subgroups of patients.

FIGURE 1.—Survival by method of diagnosis. Solid line = TUR (56 of 87 patients; dashed line = no TUR (21 of 52 patients). $P < .01$.

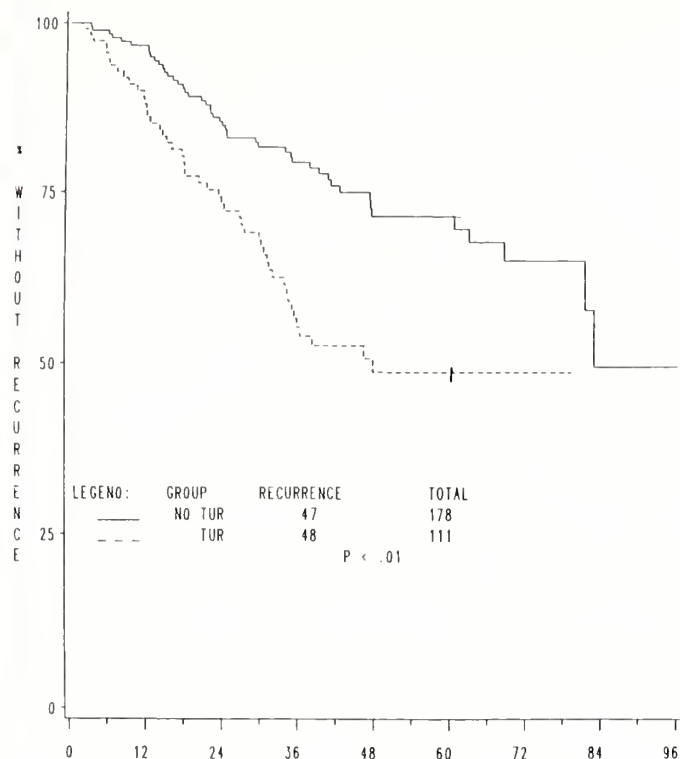


FIGURE 2.—Freedom from metastasis by method of diagnosis, RTOG 75-06.

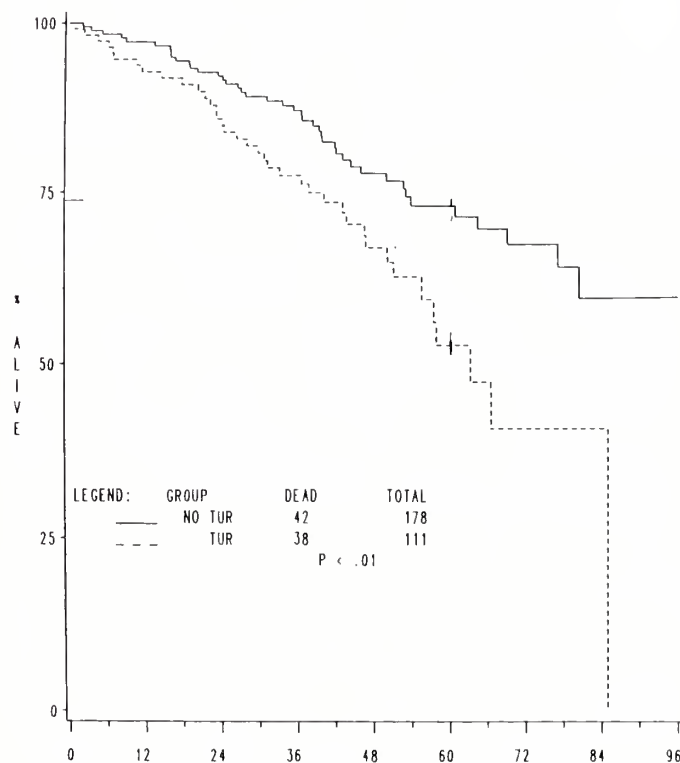


FIGURE 3.—Survival by method of diagnosis, RTOG 75-06.

TABLE 7.—Patterns of Care Outcome Studies: Adverse effect of TURP

Observed in T3, T4, or stage C cancers
Local recurrence unchanged
Metastatic recurrence doubled
Death rate doubled
Not explained by differences in histology or tumor extent

National Averages for Survival

The survival of 60 patients with mixed stages A1 and A2 disease treated in 1973–1974 in the United States is shown in figure 4 to be equal to survival for their expected age group (16). One patient experienced an isolated local recurrence, and 3 patients developed metastasis as a first failure. No lymph node dissections were performed, and patients were not selected for favorable functional status as is common in surgical reports.

The national averages for survival of stage B patients are shown in figure 5 (16); no patient had lymph node staging. No significant decrease in survival was observed over that expected for a similar age group of patients without cancers at 5 years, but a 15% decrement is noted at 10 years. Again, these patients are not selected for favorable prognostic indicators. Figure 6 shows the national average for survival of patients with stage C cancer. Increased mortality was expressed in the first 5 years with a 25% decrement below the expected survival at both 5 and 10 years (16). This is a population that is neither selected for its good general health nor assessed by lymph node dissection.

Improvement in Survival Between 1973 and 1978

The survival of stage B patients treated in 1973 and in 1978 shows improvement (fig. 7), but the difference is not

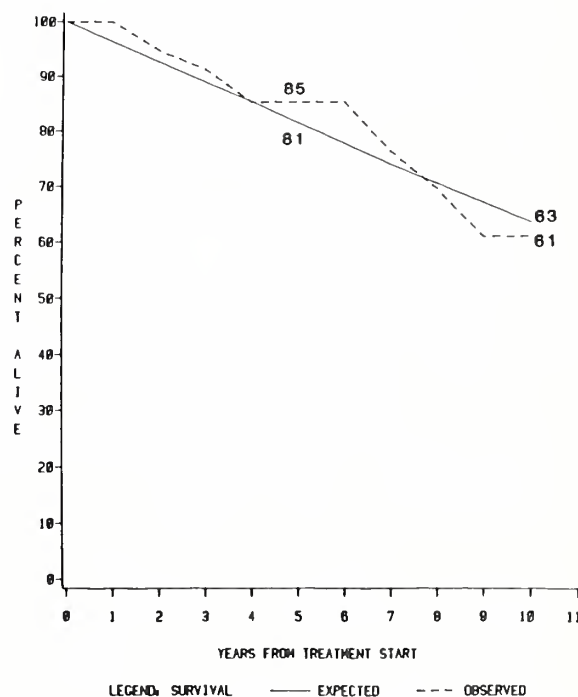


FIGURE 4.—National averages: Stage A survival compared with expected survival (60 patients).

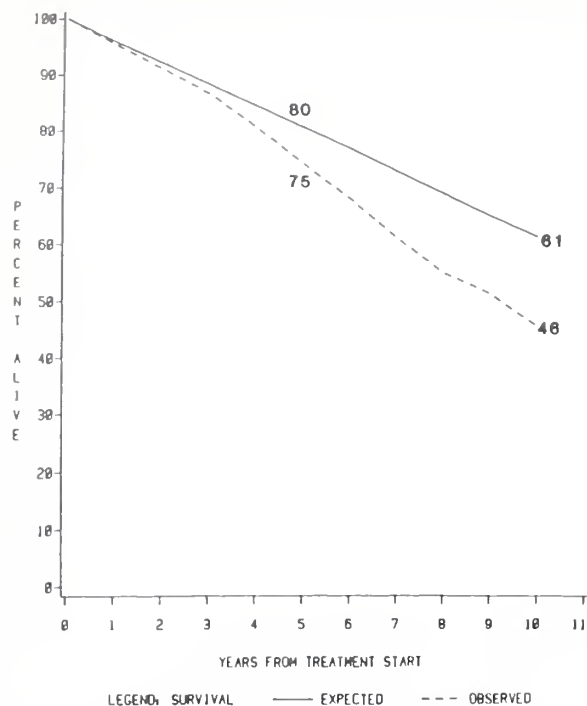


FIGURE 5.—National averages: Stage B survival compared with expected survival (312 patients).

significant and was predicted when we compared the distribution of favorable independent variables for survival between the 2 series (4,7). Figure 8 illustrates the difference in survival of stage C patients who were treated in 1973 versus 1978 (4) that approaches statistical significance ($P=$

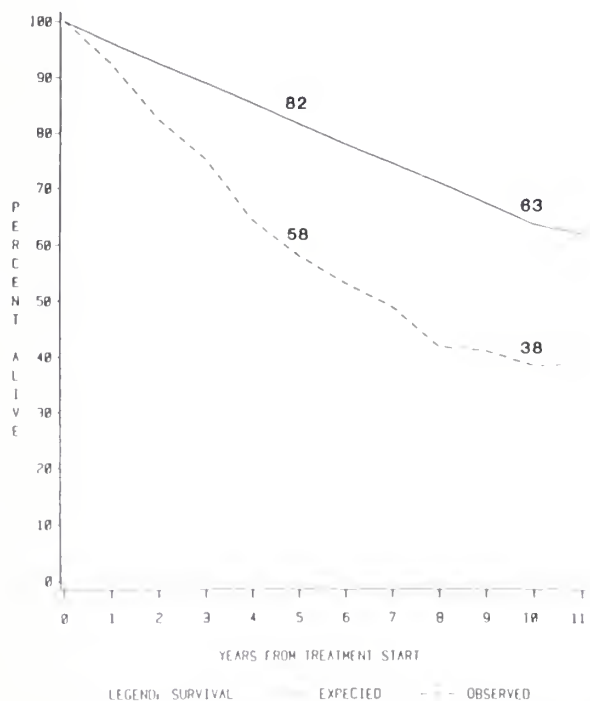


FIGURE 6.—National averages: Stage C survival compared with expected survival (296 patients).

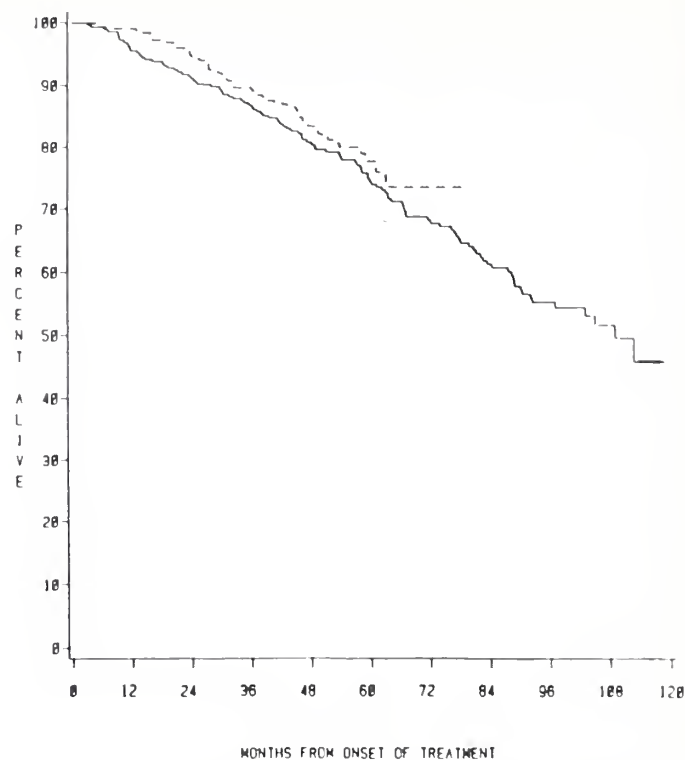


FIGURE 7.—Survival for stage B patients treated in 1973 and 1974 (312) compared with those treated in 1978 (347). Solid line = 1973; dashed line = 1978.

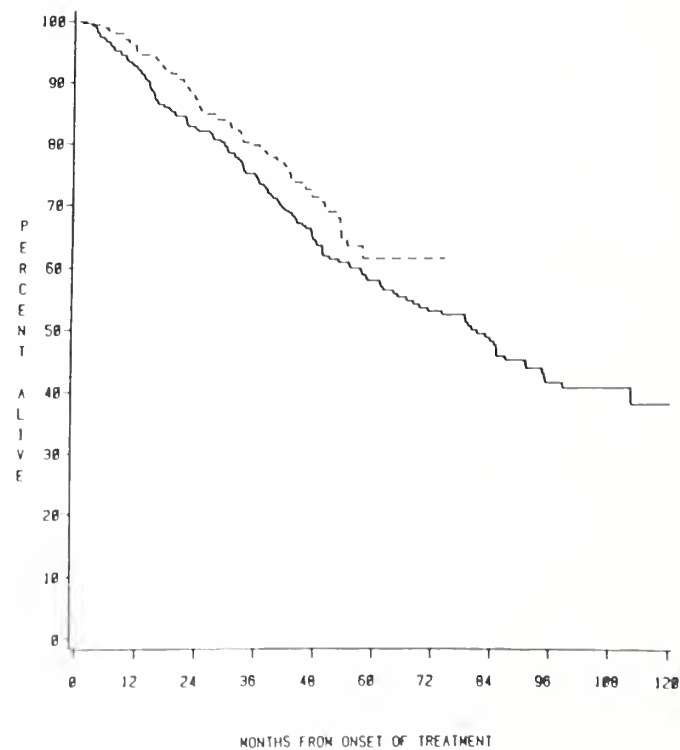


FIGURE 8.—Survival for stage C patients treated in 1973 and 1974 (296) compared with those treated in 1978 (215). Solid line = 1973; dashed line = 1978.

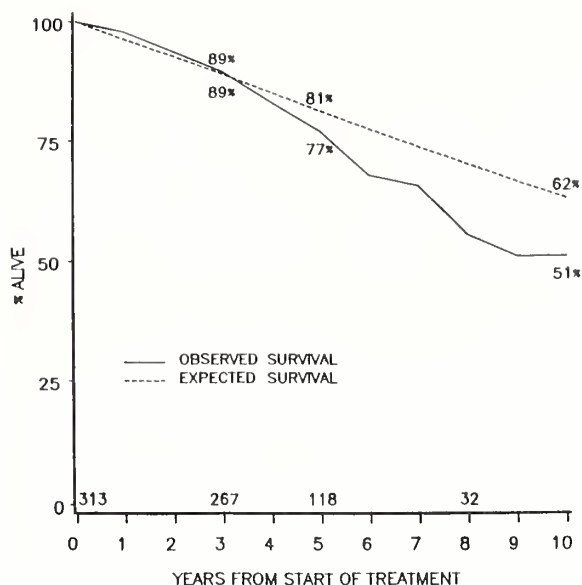


FIGURE 9.—Survival of T1 N0 M0 patients treated with external-beam irradiation.

.10). When we analyzed the distribution of independent variables for survival between these 2 series, we saw no difference to explain the improved survival, and it may well be due to improved treatment. Stage migration is always a concern in sequential studies but is difficult to rule in or out (17).

Survival of a Subgroup of Early Stage B Patients

The survival data of 313 early stage B (T1 N0 M0) patients (shown in fig. 9) represent a pool of data from 138 treated in 1973 and followed up to 10 years with 175 treated in 1978 and followed up to 5 years (18). There is no significant difference from the expected survival at 5 years, although a 10% decrement is noted at 10 years. Indeed, this would be expected as no patient had a lymph node dissection, and 30% of 40 patients with grade III histology developed metastasis as a first failure site.

Outcome for Groups of Patients Directly Comparable to Surgical Series

Table 8 shows the outcome of 65 patients treated in 1978 who were given external-beam irradiation or ¹²⁵I implants after negative lymph node dissection. They did extremely well in local control, with 1 of 65 patients experiencing isolated local recurrence, and any type of recurrence was noted in only 9 of 65 patients (14%).

A comparison of the survival of the subgroup of patients treated with external-beam irradiation with that of patients in the randomized study of the Uro-Oncology Research Group

as reported by Paulson et al. is presented in figure 10 (19). Patients in the Patterns of Care Study show the same nonprogression rate as those in the surgical arm of the Uro-Oncology Research Group study. Patients in this latter group who received radiation therapy remain anomalous and exhibit a disease progression rate commonly seen in stage C patients.

Table 9 lists the serious problems of the investigation, analysis, and reporting of the Uro-Oncology Research Group study that inevitably lead the observer to the conclusion that the radiation arm contained stage C patients, whereas the surgical arm contained lower stage patients (20,21). It is unfortunate that this trial (19) has been reported to show that radical prostatectomy is superior to external-beam radiation therapy.

Sequelae of External-beam Radiation Therapy

Table 10 lists the posttreatment sequelae observed in 1,393 patients treated with external-beam radiation therapy. There was indeed only 1 death among 1,393 patients, and these complications were observed for treatment given to patients in 1973, 1974, and 1978. It is clear that current modern technology and technique will result in even fewer serious complications.

To keep in perspective the comparable sequelae, we have included data from several recent surgical series in table 11 (22-25).

The maintenance of potency after treatment is a most important goal, and table 12 illustrates that potency is generally more frequently preserved following external-beam radiation therapy than following radical prostatectomy even with nerve-sparing modification (26,27). This is even more impressive when you consider that the radiation group is an unselected group of patients who frequently have other medical illnesses and variable levels of general health, whereas the radical prostatectomy group is highly selected for both general health and desire to maintain potency.

Adjuvant Irradiation After Prostatectomy for Pathologic Stage C Cancer

Table 13 illustrates the clinical inaccuracy of one's judging the extent of prostate cancer among patients in various institutions as evaluated by the overall fraction of surgical patients who have pathologic stage C cancer. It also reflects a variation in the tendency of surgeons to operate on patients with stage B2 cancer (e.g., Catalona 44%, Walsh 22%), when they will indeed observe the predicted two-thirds frequency of extension out of the gland (26-28).

In tables 14 and 15, we (29) have tabulated the local control of prostate cancer when adjuvant irradiation was given before or after local recurrence. Control is obtained in 94% of

TABLE 8.—Results of 65 patients with stages A and B after negative lymph node dissection

Treatment group	Stage		Failure			Total failure	
	A	B	Isolated infield	Infield and metastases	Metastases	No.	Percent
External-beam irradiation	10	27	1	1	3	5	14
¹²⁵ I implant	5	23	0	3	1	4	14

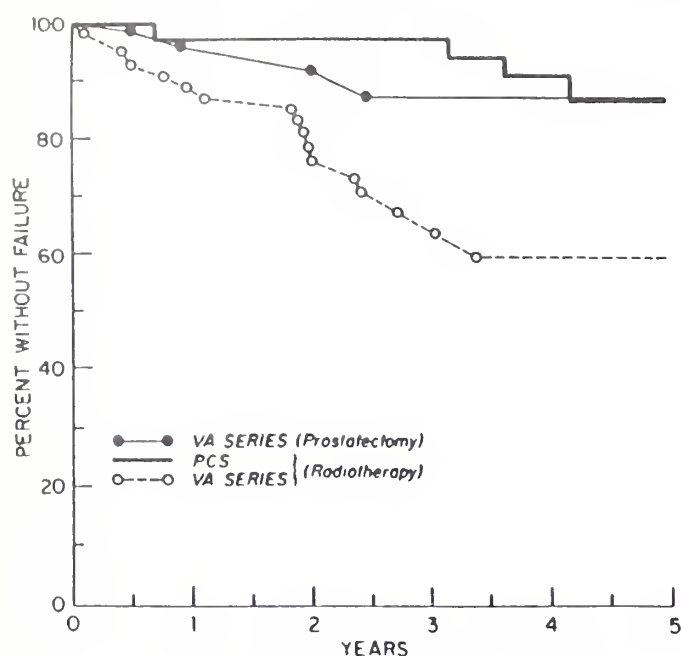


FIGURE 10.—Comparison of Patterns of Care Study (PCS) series (stage A2, B with negative lymph node dissection) to Uro-Oncology Research Group trial.

the patients when treated shortly after surgery versus 70% of patients when treated after clinical recurrence. It is also commonly observed that higher doses of radiation are required after clinical recurrence and more complications will result from that high-dose treatment.

Table 16 is a summary of local recurrence reported in 943 patients with pathologic stage C cancer categorized by

TABLE 9.—Problems of the study, analysis, and reporting of the Uro-Oncology Research Group comparison^a

Many lost or dead of intercurrent disease (56%) in 4-7 yr
Incontinence rate of 12%-40%
Radiation therapy committee not involved in data analysis
Suggestions of radiation therapy committee ignored
Inappropriate end point
Questionable method of randomization
Assigned treatment received by 90 of 106 (85%)
Radiation received by 4 of 47 assigned surgery
Surgery received by 3 to 59 assigned radiation
Positive surgical margins eliminated (2 patients)

^a See (19).

TABLE 10.—Complications of external-beam radiation therapy

No. of patients treated	Year of treatment	Percent free of complications (actuarial) at:		Actual complications from:			
		5 yr	10 yr	Radiation		Surgery	
				No. of patients	Per-cent	No. of patients	Per-cent
619	1973, 1974	93	86	28	4.5	16	2.5
674	1978	92		40	6.0	17	2.5

TABLE 11.—Complications of radical prostatectomy^a

Complication	Frequency, %
Death	0-2
Infection, fistula, rectal injury	1-8
Bladder stricture	9-18
Incontinence	2.5-15
Impotence	90-100

^a No complications involving the lymphatic system were observed. See (22-25).

treatment (adjuvant irradiation); a consistent reduction in local recurrence was noted when postoperative radiation was given.

The reason no differences are reported in survival between the irradiated and nonirradiated pathologic stage C patients may be explained. With reasonable basic assumptions (30% develop metastasis in 5 yr, 15% die of intercurrent disease in 5 yr, and 5% develop local recurrences after irradiation, but 23% do so without it), it is possible for one to calculate that 150 patients would be needed in each experimental arm to show the difference in a prospective random comparison.

Relative Costs of Radical Prostatectomy and External-beam Radiation Therapy

Table 17 illustrates that the surgical treatment of early prostate cancer doubles the cost of treatment whether it is radical prostatectomy or lymph node dissection with ¹²⁵I seed implantation (5). Equivalent survival results are obtained with external-beam radiation therapy and either of the techniques mentioned before. This escalation of cost may not escape the notice of perceptive analysts at health maintenance organizations, insurance companies, and the Federal Government who are approving payment of the bills for this care.

Future Research

Patterns of care studies are needed in the surgical treatment of prostate cancer so that physicians can observe what the national averages are for outcome and whether differences exist in success of treatment in different types of facilities. Are the good results observed in five or six reporting institutions also obtained in the usual community hospitals?

TABLE 12.—Maintenance of potency after treatment

Treatment	Potent, %
Previous	
Standard radical prostatectomy	0-10
External-beam radiation therapy	60-70
Recent	
Nerve-sparing prostatectomy ^a	72
Nerve-sparing prostatectomy ^b	52
External-beam therapy ^c	
<3/mo, partial erections	47
≥3/mo, full erections	73

^a See (26).

^b See (27).

^c Banker FL: Personal communication.

TABLE 13.—Frequency of pathologic stage C disease observed in patients having radical prostatectomies

Institution reporting	Reference	No. of prostatectomies performed	No. of patients with pathologic stage C	Frequency, %
The Johns Hopkins Hospital	(26)	100	41	41
Barnes Hospital	(27)	77	35	45
Virginia Mason Medical Center	(28)	148	45	30
Duke University Hospital ^a		319	159	50

^a Anscher MS, Prosnitz LR: Submitted for publication.

TABLE 14.—Postprostatectomy radiation therapy before local recurrence

Principal investigator	Reference	No. locally controlled/ No. of patients	Five-yr survival, %	Follow-up, yr
Ray	(30)	10/13	57	3–15+
Pilepich	(31)	18/18	~45	1–10
Rosen	(32)	15/16	~94	7 (median)
Gibbons	(28)	21/22	~73	5–15
Hanks	(29)	10/10	86	2–11
Total		74/79 (94%)		

The national averages for outcome of radiation therapy should be continuously monitored for further evidence of improvement with time and if more appropriate treatment is given with time.

Studies should be designed to test the hypothesis that TURP may disseminate cancer.

Studies should be developed that are directed at improving the rate of local control and suppressing the rate of metastasis in stage C cancer.

Urologists and radiation therapists must agree on common staging, end points of outcome reporting, and methodology of data analysis.

DISCUSSION

Problems of Comparison

Comparison of the outcome of external-beam radiation therapy and management of radical prostatectomy of clinically localized prostate cancer is confounded by the reporting of different end points and different statistical methods of analysis (including some that are incorrect and misleading), and a general absence of reporting of complications in the literature.

One of these problems of comparison is illustrated by the

frequently quoted Hopkins series (22) and the recent report of Middleton et al. (24), in which data on patients lost to follow-up are discarded and survival is calculated on those who remain. This is a misleading and an improper method of analysis of the data. As an example, data on 18% of the patients in the Hopkins series of 70 and 11% of patients in the Middleton series of 156 patients lost to follow-up were discarded and treated in this manner. The data of Gibbons et al. (23) are correctly analyzed and can be used in comparison to the long-term data reported by radiation therapists.

Surgical survival is *expected* to exceed that of equivalent treatment by irradiation as surgeons treat a generally more healthy subset of patients who will experience less intercurrent disease mortality. Our patterns of care data also show that Karnofsky functional status is an independent variable in recurrence, which means that stage for stage, patients with low Karnofsky status (included in radiation series) will more likely die of cancer.

Optimization of Technical Management With Radiation Therapy

Our studies (4,7–9) have shown that prostate cancer must be treated with high-energy linear accelerators, the use of treatment simulation, and the use of complex field arrangements and dosimetry if optimal results are to be obtained. Excessively simple treatment programs are clearly associated with increased numbers of complications or recurrence and should not be used.

As expected, we (10) believe that radiation dose is a critical determinant for obtaining local control. A significant problem in the United States as a whole has been the use of an excessive dose in early stage prostate cancer that only contributes to an excess of morbidity without improving local control. Tumor dose must be adjusted to tumor volume, and it appears that only the patients with locally extensive stage C cancers benefit from radiation doses of 7,000 cGy or more. The optimization of dose and tumor volume has been shown to offer the opportunity for significant improvements in local control and complications (4,7,10).

TABLE 15.—Postprostatectomy radiation therapy after local recurrence

Principal investigator	Reference	No. locally controlled/ No. of patients	Survival	Percent
Ray	(30)	11/19	Disease free at 5 yr	40
			Disease free at 10 yr	26
Rosen	(32)	10/13	Alive at 4 and 13 yr	15
Gibbons	(28)	16/23	Alive 5–25 yr	40 (9 of 23)
Hanks	(29)	8/10	Alive at 5 yr	71
Total		45/65 (70%)		

TABLE 16.—Effect of postoperative irradiation on local recurrence in patients with pathologic stage C prostate cancer

Treatment	Investigators at	Reference	Local recurrence	
			No irradiation	Postoperative irradiation
			No. of patients/ total No. of patients	No. of patients/ total No. of patients
Radiation and surgery	Duke University Hospital	^a	39/160	3/94
	University of Utah Medical Center	(33)	39/160	3/94
	Virginia Mason Medical Center	(28)	39/160	3/94
Radiation only	The Johns Hopkins Hospital	(34)		3/88
	Stanford University Medical Center	(30)		3/88
	Washington University Clinics	(31)		3/88
	Sacramento (author's practice)	(29)		3/88
	Joint Center for Radiation Therapy	(32)		3/88
	University of Southern California	(35)		3/88
		(36) ^b		1/45
Surgery only	Mayo Clinic	(37)	127/556	
	Memorial-Sloan Kettering Cancer Center	(38)	127/556	
	University of Virginia Hospital	(39)	127/556	
	University of California Hospital (Los Angeles)	(40)	127/556	
	Bowman Gray	(41)	127/556	
	Massachusetts General Hospital (Harvard)	(42)	127/556	
			166/716 (23%)	7/227 (3%)

^a Anscher MS, Prosnitz LR: Submitted for publication.^b Authors present an editorial comment without reference.

It is important that urologists remain aware of the subset of patients for whom an increased frequency of metastasis and death is recorded when their diagnosis has been established by TUR. This subset represents the group of intermediate and poorly differentiated stage C patients; the effect is not observed in stage B patients or those with well-differentiated tumors of any stage (7,11,12). Precisely what is responsible for this adverse outcome is not known but is subject to ongoing study. In addition to suggesting that dissemination of the cancer cells follows TURP, Hoffman et al. (43) believe that this subgroup of patients has an increased frequency of lymph node metastasis. This latter observation awaits confirmation by researchers at a second institution. Conversely, the patient who has intermediate or poorly differentiated stage C cancer who does *not* present with obstruction and does not require a TUR has a favorable prognosis, almost

equivalent to the survival of stage B patients (4). As we see reports of the management of stage C patients with various modalities, it will be important to know the distribution of patients who had undergone TURP versus needle biopsy within each series as another variable that could falsely cause treatments to appear different. In prospective studies of stage C prostate cancer, method of diagnosis should be a stratification point.

Long-term Outcome With Radiation Therapy

The survival and disease-free survival of patients (16,18) treated in the United States is excellent and approximates that of single-institution reports, even though this national average is composed of investigators who obtain results better and worse than the national average. Apparently, the technology and methodology of treatment of prostate cancer with external-beam radiation therapy have been well distributed throughout the United States, even though we have clearly identified certain types of practice and equipment that are associated with poor results. Major questions remain as to whether the technology and surgeons' expertise to perform radical prostatectomy, and particularly the nerve-sparing radical prostatectomy, have had equal distribution around the United States, and whether those complex procedures are performed with acceptable morbidity and cure in facilities outside the half-dozen from which researchers report their results in the literature.

It is possible that the improvement in survival observed in stage C patients between 1973 and 1978 is due to the improvement of therapy technique and dose selection that we (4) have shown to occur. One can never exclude the possibility that stage migration has accounted for this improvement,

TABLE 17.—Relative costs of treatment for cancer of the prostate, Sacramento, California, 1984

Treatment	Relative costs in dollars		
	Average	Treatment	Range
Lymph node dissection and ¹²⁵ I implant	13,900	12,000	10,200-26,400
Radical prostatectomy	14,100	14,400	10,000-18,900
External-beam radiation therapy			
Prior to October 1984	6,650	6,750	6,200-6,750
After October 1984 (CPT-4) ^a	5,500	5,600	5,300-5,600

^a Government-mandated billing change to CPT-4 system.

but when we evaluated the difference in survival against the distribution of independent variables in the 2 series, we found no explanation for the improved results. This is in contrast to what we have seen in stage B cancer, i.e., the improvement in results between 1973 and 1978 is explained by increased representation of low-grade tumors in 1978.

Results of Radiation Therapy in Candidates for Radical Surgery

Our studies with early stage B (T1) tumors show only a 10% decrease in survival at 10 years over that expected for this age distribution of patients, and we have also shown that, within this group of patients, there were 40 with poorly differentiated histology, of whom 30% expressed initial failure as metastasis in the first 5 years. This latter group should certainly be screened by noninvasive techniques for lymph node metastasis, but, if finding small amounts of lymph node metastasis at surgery would not alter the treatment the patient receives, then it does not seem worthwhile for the physician to proceed with lymph node dissection and its associated 10% morbidity. (Survivorship at 10 yr, which is only 10% below expected, would seem comparable to that in the surgical series equaling the 10-yr expected survival *after* all patients with lymph node metastases are eliminated.)

In our survey of patients treated in 1978, we identified 65 patients who are directly comparable to patients receiving radical surgery because their health allowed lymph node dissections; the results of those node dissections were negative. These patients show a nonprogression rate at 5 years that is the same as many radical surgery series and indeed the same as reports of the surgical arm of the Uro-Oncology Research Group prospective trial.

Morbidity of Radiation Therapy

Radiation sequelae are modest, and we know there has been a reduction in morbidity for patients treated more recently as opposed to 10–15 years ago. We would expect a similar reduction in surgical morbidity as a result of improvement in technology and general supportive care. The complications of surgery and radiation are quite different, and the patient is going to need consultation with specialists of both disciplines before he can evaluate what complications are acceptable or unacceptable and to select the procedure he wishes.

Potency appears to be better preserved after radiation therapy than after the nerve-sparing prostatectomy. Our current data indicate that 73% of truly potent patients retain their potency, and Bagshaw et al. (44) have demonstrated that over 80% of their patients retained potency. The 2 earlier reports of the nerve-sparing operation show 52% and 72% of the patients maintaining potency (26,27).

Radiation as an Adjuvant in Pathologic Stage C Patients

We have shown that it might take as many as 150 patients in each arm of a prospective random trial to demonstrate an overall advantage of administering external-beam therapy following radical prostatectomy for pathologic stage C disease. The local control rates observed in data from nearly 1,000 patients tabulated from the literature indicate a consistent difference in local recurrence of roughly 25% versus 5% when postoperative radiation is added. It also seems clear from

the literature that the patient with seminal vesicle involvement has a greater risk of local recurrence than does the patient with tumor at the surgical margins, and it would seem that these 2 groups of patients should receive adjuvant radiation therapy. The advantage of administering adjuvant therapy following maximal recovery of urinary function and before local recurrence has occurred is that doses of 6,000 cGy can be administered with a high local control rate and low morbidity. If one waits until there is gross recurrence of the cancer, then doses in the range of 7,000 cGy are needed and morbidity is markedly higher.

Research Needs

Clear research needs exist for improvement of our treatment of prostate cancer, an understanding of this cancer's particular biology, and documentation of the availability of high quality care to everyone in the United States.

For these goals to be achieved, the Federal Government and private sources must increase funding of clinical and basic research in prostate cancer to a level appropriate for this major national health problem that affects 90,000 and kills 25,000 men each year.

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Definitive Radiation Therapy in Carcinoma of the Prostate Localized to the Pelvis: Experience at the Mallinckrodt Institute of Radiology

Carlos A. Perez,^{1,*} Miljenko V. Pilepich,¹ Delia Garcia,¹ Joseph R. Simpson,¹ Fred Zivnuska,² Mary Ann Hederman¹

ABSTRACT—Definitive radiation therapy was administered to 577 patients with histologically confirmed carcinoma of the prostate localized to the pelvis between January 1967 and December 1983. All patients were available for a minimal 3-year follow-up, and the median period of observation is 6.5 years. The actuarial survival without tumor in stages A2 and B at 5 years was 78% and at 10 years 60%. In stage C, the corresponding survival figures were 60% at 5 and 40% at 10 years. The overall actuarial survival in stage B patients was 76% at 5 and 56% at 10 years, which is similar to the life expectancy of a comparable cohort of normal males. In stage C, the actuarial survival was 65% at 5 and 35% at 10 years. The pelvic failure rate in stage A2 was 12% (5 of 41), 17% in stage B (31 of 185), 28% (93 of 328) in stage C, and 48% (11 of 23) in stage D1. Distant metastases were noted in 12% of the patients with stage A2, 20% stage B, 42% stage C, and 65% stage D1. In stage B, patients who had control of the pelvic tumor exhibited an 85% actuarial 5-year survival and a 60% one at 10 years. This compares with an actuarial survival of 30% at 5 and 10 years when there was evidence of pelvic recurrence alone or combined with distant metastases. In stage C patients with pelvic tumor control, actuarial survival was 81% at 5 and 50% at 10 years, in comparison with 25% at 5 and 10% at 10 years when there was development of pelvic recurrence or distant metastases or a combination of both. There was a strong correlation between the survival and appearance of distant metastases with the histologic degree of differentiation of the tumor in all stages. However, the probability of tumor control in the pelvis was not significantly correlated with this parameter. The administration of hormones concomitantly with radiation therapy did not significantly influence the probability of tumor control, appearance of distant metastases, or survival. Major sequelae of therapy were noted in 2.2% of the patients, whereas minor sequelae were observed in approximately 12% of the patients. Radiation therapy has been shown to be an effective therapeutic alternative to radical prostatectomy or hormonal manipulation in patients with carcinoma of the prostate.—NCI Monogr 7:85-94, 1988.

Over the past 25 years, radiation therapy has been demonstrated to be an acceptable therapeutic alternative for patients with stages A2, B, and C carcinoma of the prostate. The survival and tumor control are comparable to those observed with radical prostatectomy in patients with early stages and hormonal manipulation or orchiectomy, or both, for more advanced stages. Sequelae of treatment have been acceptable with a good quality of life in most patients (1-6).

¹ Radiation Oncology Center, Mallinckrodt Institute of Radiology, Washington University School of Medicine, Missouri Baptist Hospital, and St. Luke's Hospital, St. Louis, MO.

² St. John's Mercy Medical Center, St. Louis, MO.

* Reprint requests to: Carlos A. Perez, M.D., Radiation Oncology Center, Mallinckrodt Institute of Radiology, Suite 411, 4511 Forest Park Blvd., St. Louis, MO 63108.

PATIENTS AND METHODS

Patients.—Between January 1967 and December 1983, a total of 577 patients with histologically proven adenocarcinoma of the prostate localized to the pelvis were treated with definitive radiation therapy at the Radiation Oncology Center of the Mallinckrodt Institute of Radiology and affiliated hospitals. All patients have been followed for a maximum of 16 years, minimum of 3 years, with a median follow-up of 6.5 years. All radiation oncology and hospital records were reviewed as required, and the information was coded on computer-compatible forms and analyzed on a VAX 8600 computer. A Biomedical Department Program statistical package was used for computation of the data (7,8). All survivals and survival functions utilize the actuarial life table as applied by Cutler and Ederer (9), and test statistics provided are Generalized Wilcoxon (Breslow), Generalized Savage (Mantel-Cox), and Tarone-Ware (10,11). Trend analysis was performed by the Tarone method (12).

Each patient had a complete physical examination, rectal examination, routine blood count, chemistry profile, urinalysis, and determination of serum prostatic and acid phosphatases as well as alkaline phosphatases. Chest x-ray, intravenous pyelogram, and radioisotope bone scan were also obtained. Initially, the regional lymph nodes were evaluated by pedal lymphangiogram, but later this was replaced by computed tomography scans of the pelvis and abdomen. The patients were staged according to a modification of the American Urological Association classification of 1978 (table 1). Cystoscopy was routinely performed; in most patients, the diagnosis was obtained by needle biopsy, although in about 25% of them, transurethral resection of the prostate provided definitive diagnosis. The tumors were classified according to the degree of histologic differentiation into well, moderately, or poorly differentiated (table 2).

Patients were followed periodically during and after therapy or until death by the staff of the Radiation Oncology Center, the referring urologist, and occasionally the family physician. When follow-up information was not available, contact was made directly with the patient or relatives.

Follow-up was obtained in 98% of the patients, and those lost to follow-up were considered to have died of the disease.

Tumor control was assessed by periodic rectal examination, acid phosphatase plasma determinations, and, when indicated, radiographic or radionuclide scan studies. Initially, surgeons performed postirradiation biopsy of the prostate on each patient almost routinely to ascertain the effect of radiation on the tumor. However, later this procedure was limited only to patients suspected of recurrence following rectal

TABLE 1.—Clinical staging of carcinoma of the prostate^a

Stage	Description
A1	Well-differentiated tumor, incidental finding
A2	Poorly differentiated tumor, or more than 5% positive chips found on transurethral resection; incidental finding
B1	Tumor < 1.5 cm in diameter or localized to one lobe
B2	Tumor > 1.5 cm in diameter or extending beyond one lobe
C1	Tumor extending into periprostatic tissues; normal to high acid phosphatase levels
C2	Tumor invading seminal vesicles or periprostatic extension, diameter of > 6 cm
D1	Tumor extension into bladder or rectum, pelvic disease extending to pelvic wall
D2	Abnormal bone scan or survey or distant metastases

^a This is the staging system used at the Radiation Oncology Center of the Mallinckrodt Institute of Radiology, which is modified from the American Urological Association Classification of 1978.

examination (tumor persistence over 18 mo after irradiation or evidence of regrowth).

Irradiation techniques.—The methods of treatment with either 22-megavolt photons from a betatron or 16- to 25-megavolt photons from linear accelerators have been described (13). With the betatron, the pelvic tissues received 4,500–5,000 cGy through anterior/posterior–posterior/anterior ports (15 × 15 cm for stage B or 18 × 15 cm for stages C and D1 tumors). Following this, the posterior port was discontinued and the anterior port decreased to 14 × 14 cm to deliver an additional 1,000 cGy to the external iliac and hypogastric lymph nodes. The anterior/posterior port was further reduced to 6 × 8 cm or 8 × 10 cm (depending on the size of the prostate) for an additional 1,000 cGy, for a total dose of 6,000–6,500 cGy to patients in stages A2 and B or 7,000 cGy to those in stage C.

In 1974, a 25-megavolt photon beam from a linear accelerator was used, and after 4,500 cGy was delivered through a large anterior/posterior–posterior/anterior port, an additional 2,000–2,500 cGy were delivered with 270° anterior

TABLE 2.—Distribution of patients by clinical stage and pathologic tumor differentiation

Degree of differentiation	Stage			
	A2	B	C	D1
Well	12	78	90	3
Moderate	18	78	131	4
Poor or undifferentiated	10	27	102	14
Ungraded	1	2	5	2
Total	41	185	328	23

arc rotation (7 × 9- or 8 × 10-cm ports). Starting in 1980, the rotational boost was given with bilateral 120° arcs, with 60° skipped vectors anteriorly and posteriorly.

In a few patients, when there was lymphangiographic or surgical evidence of periaortic lymph node metastasis, this volume was treated with a dose of 5,000 cGy in 5 to 6 weeks through anterior/posterior–posterior/anterior ports.

The usual daily dose was 180 cGy in 5 weekly fractions. In a small number of patients, irradiation was temporarily discontinued for 1–2 weeks after the 4 or 5 weeks of treatment because of acute side effects (acute cystitis, proctitis, skin reaction, etc.).

RESULTS

Survival

The overall, actuarial, tumor-free survival according to the various stages of the disease is illustrated in figure 1. In stage B, a 5-year 75% actuarial tumor-free survival and a 10-year 55% rate are similar to the normal life expectancy observed in a comparable cohort of individuals (fig. 2A). In stage C, the 5-year survival was 65% and at 10 years 35%, which is approximately 10%–15% below the normal life expectancy (fig. 2B). Tables 3 and 4 illustrate the direct and adjusted survival for intercurrent disease in patients available for 5 or 10 years of evaluation, respectively. The survival figures closely parallel those noted in the actuarial survival computations. There was a strong correlation between the

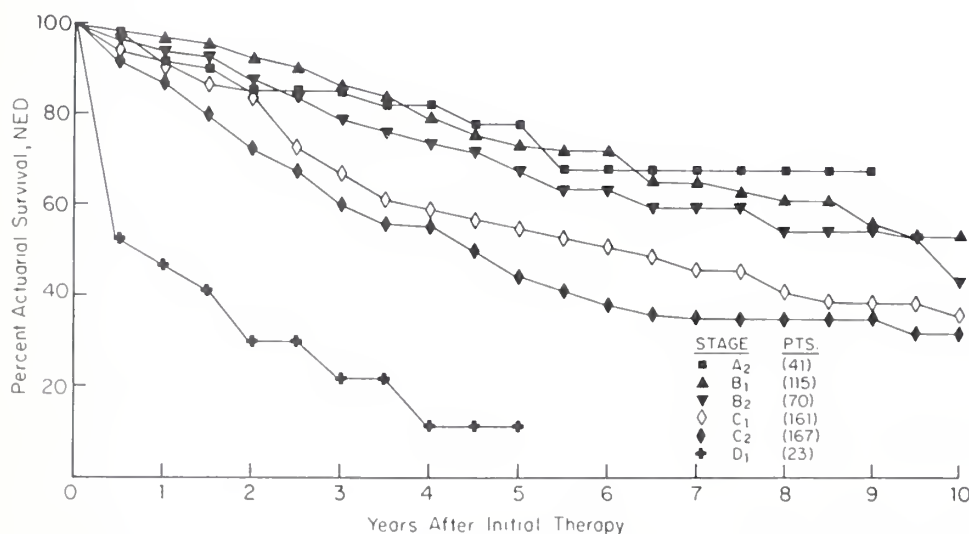


FIGURE 1.—Tumor-free actuarial (NED) survival by stage for 577 patients with carcinoma of the prostate localized to the pelvis and treated with definitive irradiation at the Mallinckrodt Institute of Radiology.

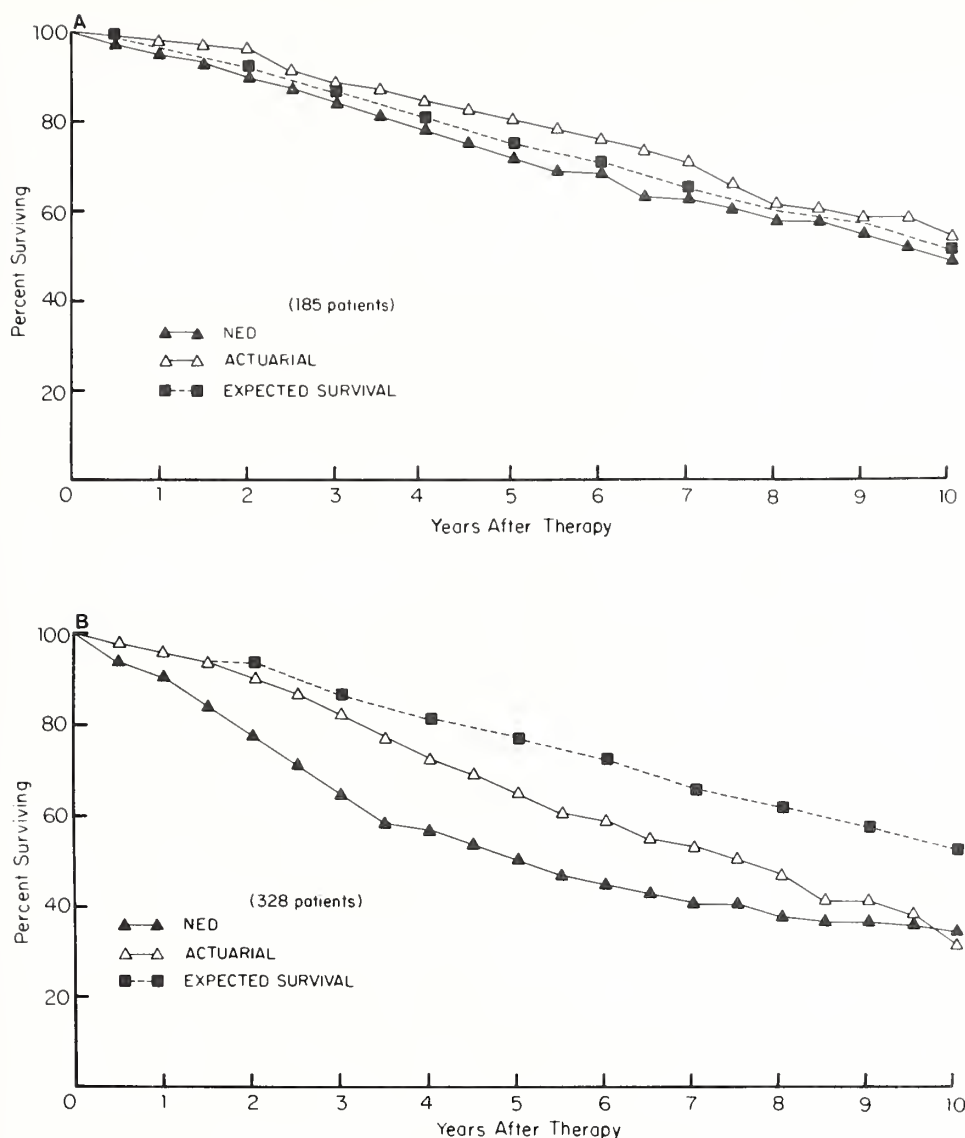


FIGURE 2.—Survival for 185 stage B patients (A) and 328 stage C patients (B) with carcinoma of the prostate localized to the pelvis and comparison with normal life expectancy. NED = no evidence of disease.

probability of survival and the histologic degree of tumor differentiation (fig. 3).

Seventy-five patients in this series had a staging lymphadenectomy prior to the initiation of radiation therapy (37 stage B and 38 stage C, of whom 6 and 15 had positive nodes, respectively). The incidence of positive nodes was similar to

that reported in other studies (14). The relapse-free actuarial survival in stage B is comparable to that for patients with negative nodes (fig. 4A). However in stage C, the actuarial 10-year survival was 85% in the 23 patients with negative nodes in contrast to only 17% in 15 patients with positive nodes (fig. 4B).

TABLE 3.—Survival at 5 yr

Clinical stage	No. of patients at risk	Five-yr direct survival		Death-intercurrent disease	Percent adjusted survival
		No.	Percent		
A2	29	23	79.3	1	82.1
B1	94	75	79.8	12	91.5
B2	51	42	82.3	4	89.4
C1	133	89	66.9	17	76.7
C2	126	80	63.5	11	69.6
D1	21	2	9.5	3	11.1

TABLE 4.—Survival at 10 yr

Clinical stage	No. of patients at risk	Ten-yr direct survival		Death-intercurrent disease	Percent adjusted survival
		No.	Percent		
A2	3	2	66.7	1	100.0
B1	30	21	70.0	2	75.0
B2	16	10	62.5	4	83.3
C1	76	30	39.5	16	50.0
C2	61	20	32.8	10	39.2
D1	12	2	16.7	2	20.0

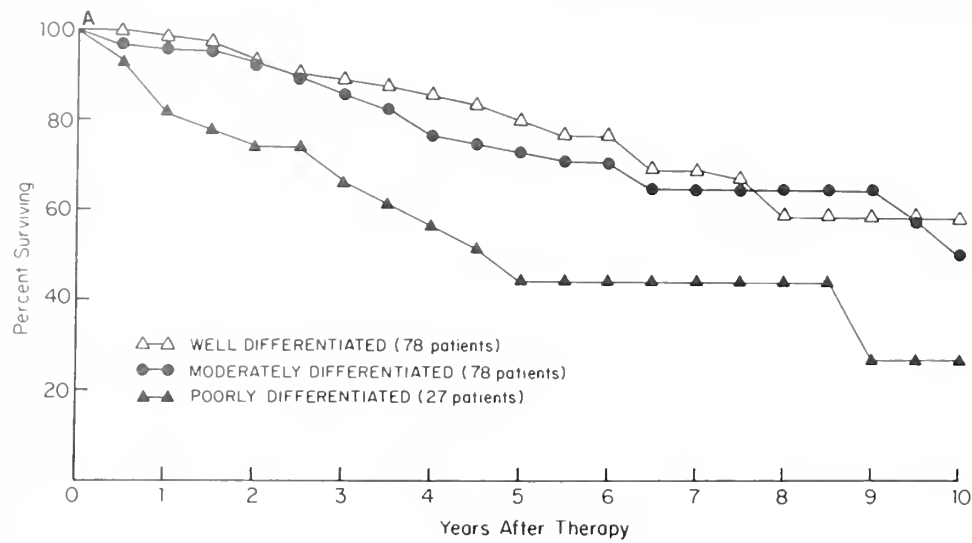


FIGURE 3.—Tumor-free actuarial survival by histologic grade for patients with stage B (A) and stage C (B) disease.

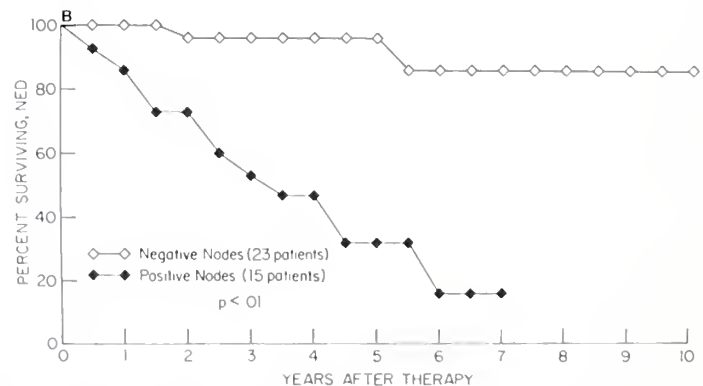
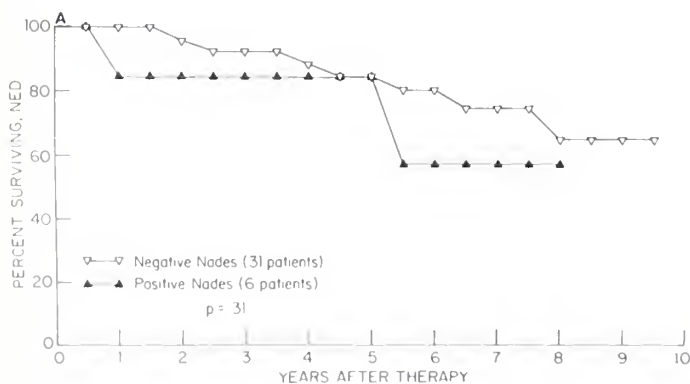
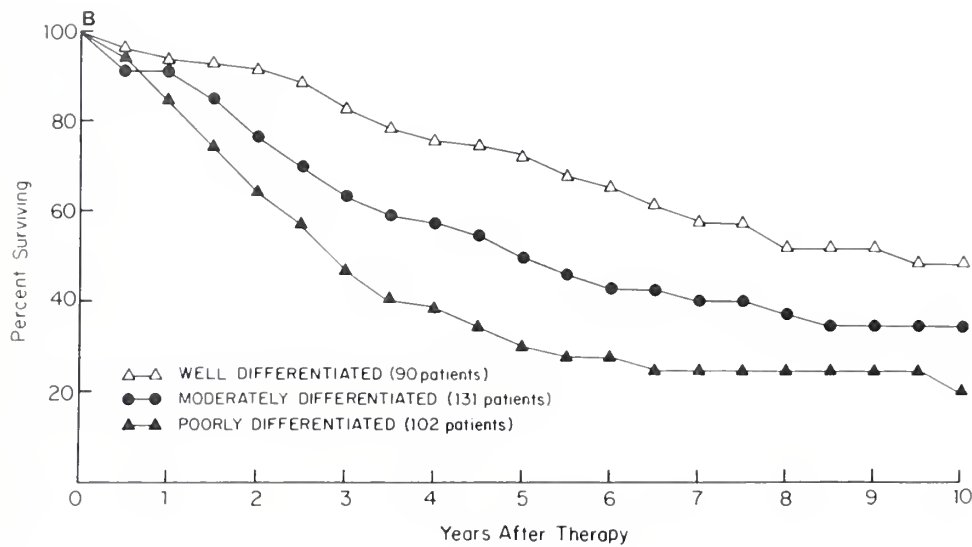


FIGURE 4.—Relapse-free actuarial survival according to lymph node status in 37 patients with stage B (A) and 38 with stage C disease (B).

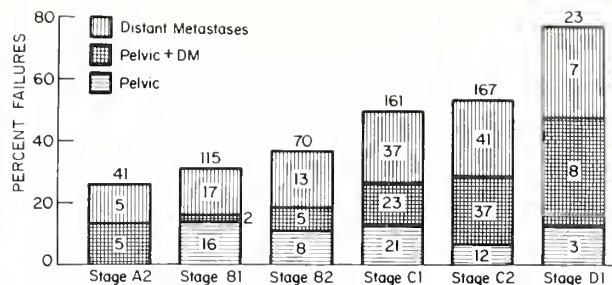


FIGURE 5.—Anatomical sites of postirradiation failure by stage. DM = distant metastases.

Anatomical Sites of Posttreatment Failure

The overall local recurrence rate was 12% in stage A2, 17% in stage B, 28% in stage C, and 50% in stage D1. Distant metastases (combined with a pelvic failure in about one-third of the patients with recurrence) were noted in 12% of the patients with stage A2, 22% with stage B, 42% with stage C,

and 65% with D1 tumors (fig. 5). Eighty percent of the local recurrences and distant metastases developed within 5 years from therapy in patients with stages A2 and B tumors. In stage C, a continuous accumulation of local recurrences and distant metastases is observed even after 5 years without any leveling of the failures. Twenty percent of the distant metastases were first noted after 5 years posttreatment, particularly in patients with stage C tumors.

Correlation of Tumor Control in the Pelvis and Prognosis

Previous analyses showed no significant correlation between the degree of tumor regression 3 months after completion of therapy and the probability of tumor control in the pelvis or survival (15). Distant metastases were noted more frequently in patients with stage C tumors who had less than 50% tumor regression (15).

However, a statistically significant better survival was observed in patients with stage B or C tumors in whom the tumor was controlled in the pelvis and who had no evidence of distant dissemination (fig. 6). In patients with stage B, the

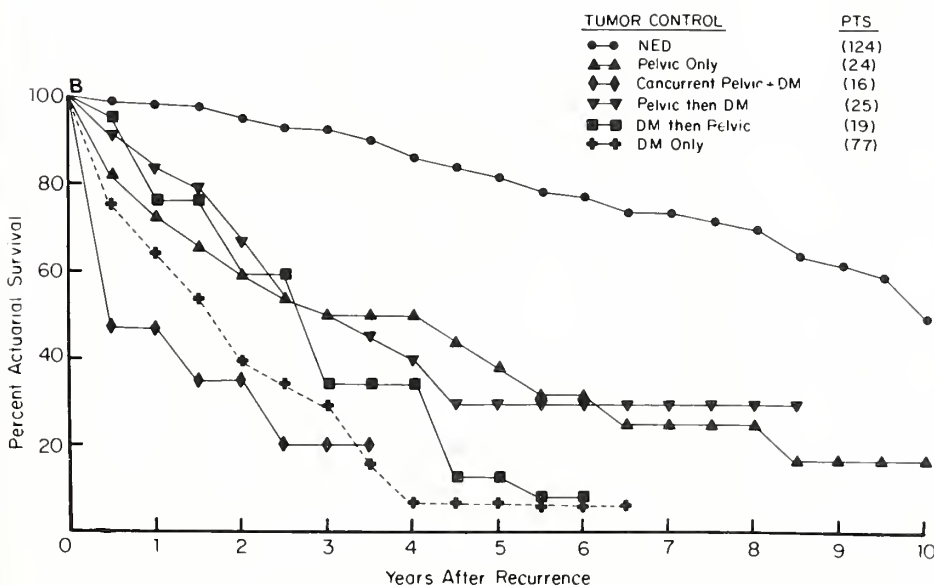
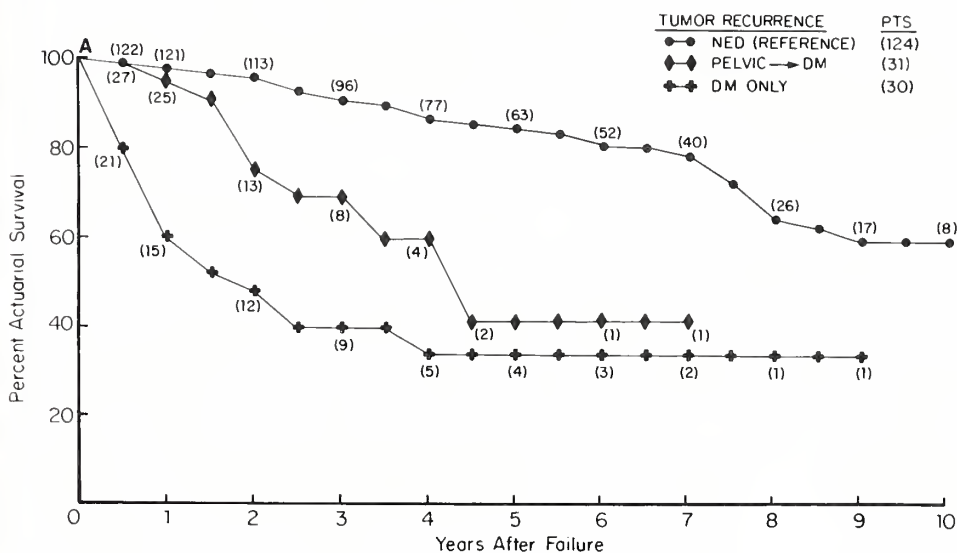


FIGURE 6.—Actuarial survival after failure for patients with stage B (A) and stage C (B) carcinoma of the prostate.

probability of survival after failure in the prostate alone in 24 patients was 35% because most of them developed distant metastases later. For patients who had an initial distant failure, alone or combined with pelvic recurrence, the 5-year survival probability was 25%. Patients with stage C tumors and pelvic failure, distally or in combinations, had a 5%-10% probability of survival.

Of the stage B patients without pelvic recurrence, 20% developed distant metastases (30 of 154), which is comparable to those who had a pelvic failure with or without distant metastases (7 of 31). However, in stage C patients without a pelvic failure, 78 of 235 had significantly less distant metastases (33%) in comparison with 60 of 93 patients (65%) with pelvic failure alone or with concomitant distant metastases ($P=.81$ and $P<.01$, respectively) as shown in figure 7.

Tumor Control and Survival Correlated With Concomitant Hormonal Therapy

The concomitant use of hormonal manipulation, either orchiectomy, administration of exogenous estrogens (usually 3-5 mg diethylstilbestrol daily), or both, in conjunction with radiation therapy, had no significant impact on the incidence of pelvic recurrence, distant metastases, or survival (fig. 8,9).

Causes of Death

The cause of death was known to be related to tumor in 140 patients, to myocardial infarction or cerebral or other vascular accidents in 50, and in 53 to other intercurrent diseases or senility (table 5).

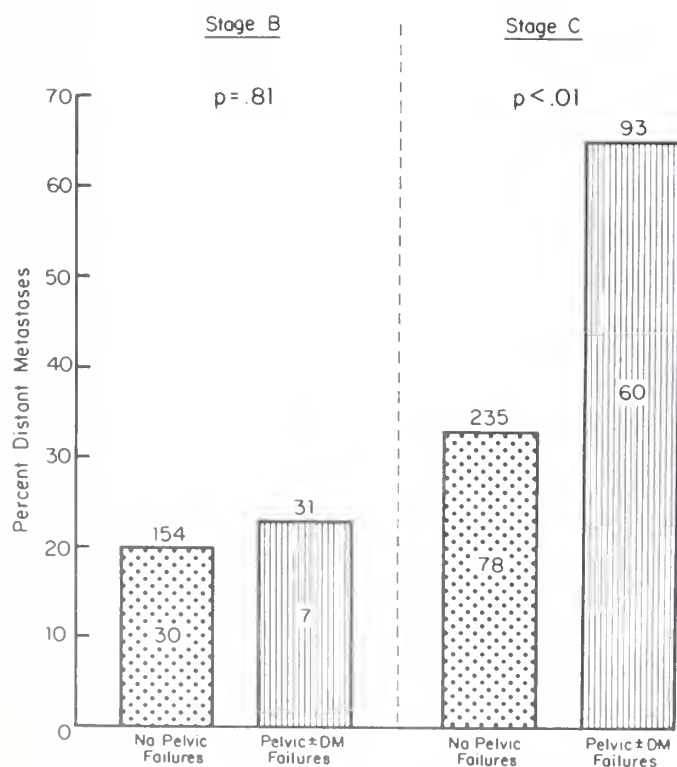


FIGURE 7. Incidence of distant metastases (DM) correlated with pelvic tumor control for patients with stages B and C disease. In stage C, the difference is statistically significant ($P<.01$).

TABLE 5.—Causes of death

Disease	No. of patients
Cerebrovascular accident	14
Myocardial infarction	23
Other vascular accidents	13
Other or unknown	53
Tumor	140
Site of failure	
Pelvis	14
Pelvis and distant metastases	59
Distant metastases only	67

Correlation of Technical Parameters With Tumor Control in the Pelvis

Patients at various times received slightly varying doses of irradiation because of some changes in technique and calibration procedures or differing philosophy of treatment over the 20 years of analysis. Figure 10 illustrates that 4 of 13 patients with stage B (31%) receiving less than 6,000 cGy developed a pelvic failure, compared with 27 of 172 patients (16%) who developed local recurrence with higher doses ($P=.24$), but 20 of 50 patients (40%) with stage C tumors treated with less than 6,500 cGy developed a pelvic recurrence, in comparison to 73 of 278 (27%) treated with 7,000 cGy. These differences are almost statistically significant ($P=.07$).

No significant correlation was seen between the doses of irradiation given to patients in stage B and survival. At 5 years, the disease-free survival in the patients in stage C receiving 7,000 cGy was 50% compared with approximately 40% of those treated with doses between 6,000 and 6,500 cGy. However at 10 years, the difference was not significant between the 2 groups (data not shown).

There was no significant correlation of the tumor control and the size of the reduced fields used for the prostatic boost in either stage B or C tumors (6 × 8-cm, 7 × 9-cm, or 8 × 10-cm ports).

Sequelae of Therapy

Major sequelae of irradiation were noted in 13 patients (2.2%), consisting mostly of small bowel obstruction (4), vesical fistula (2), hemorrhagic cystitis (2), and ureteral stricture (2). One patient treated in 1968 with anterior reducing portals received 7,800 cGy to the pubic bone and developed localized bone necrosis about the pubic symphysis (table 6).

TABLE 6.—Major definitive complications from radiation therapy in 577 patients

Complications	No. occurring
Small bowel obstruction	4
Proctitis requiring a colostomy	1
Fatal enteritis ^a	1
Rectovesical fistula ^b	2
Cystitis	2
Bladder fistula	1
Ureteral stricture	2
Pubic bone necrosis	1

^a This acute syndrome developed after a total dose of 4,020 cGy.

^b One patient also had a recurrent pelvic tumor.

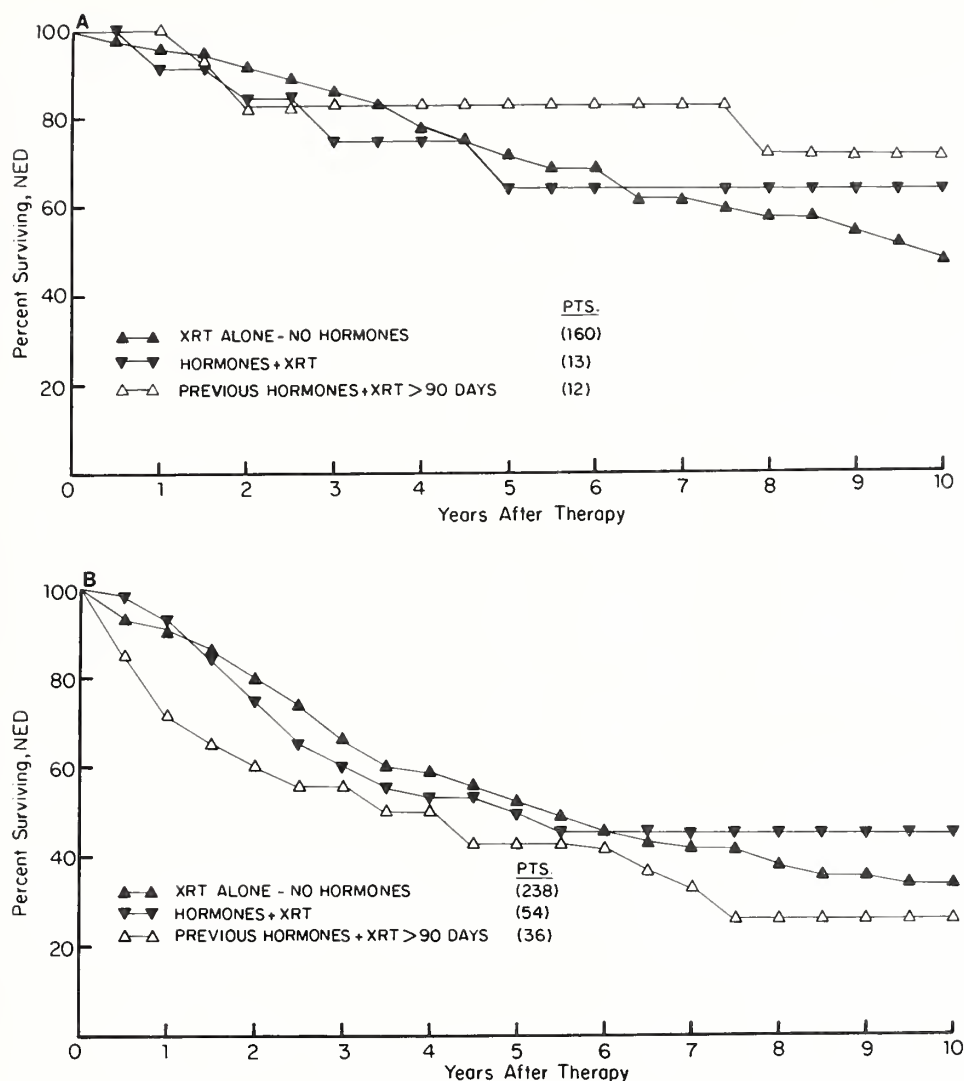


FIGURE 8.—Tumor-free survival for patients with stage B (A) and stage C (B) disease correlated with concomitant hormonal therapy.

Minor sequelae of therapy (table 7) were noted in approximately 12% of the patients and consisted of transient proctitis and hemorrhagic cystitis; a few patients experienced other gastrointestinal side effects and were treated conservatively. Urethral stricture was noted in 4.9% of the patients on whom

a transurethral resection was performed in contrast to 3.6% of those not undergoing this procedure. Leg edema was observed in 8 of 83 (9.6%) patients on whom a staging laparotomy was performed, compared with 1 of 494 (0.2%) without this procedure. Impotence was noted in 82 of 210 patients (39%) recorded to be potent prior to initiation of radiation therapy.

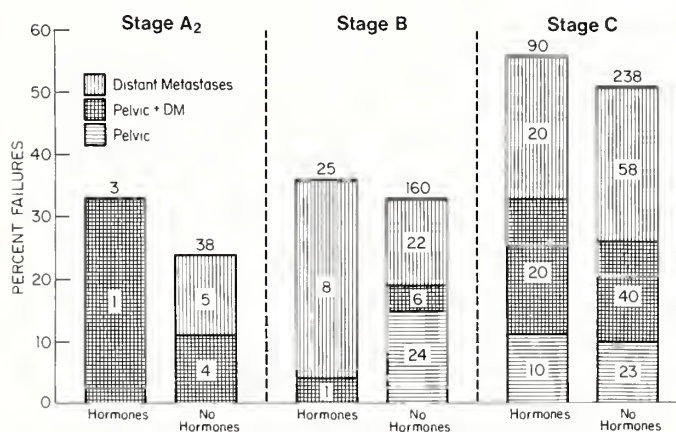


FIGURE 9.—Patterns of failure correlated with concomitant hormonal therapy for stages A₂, B, and C tumors.

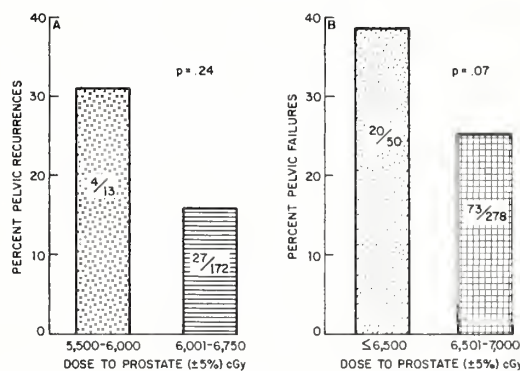


FIGURE 10.—Correlation of pelvic recurrence and dose of irradiation for patients with stages B (A) and C (B) carcinoma of the prostate.

TABLE 7.—Minor definitive complications from radiation therapy in 577 patients

Complications	No. occurring
Proctitis	29
Rectal ulcer	1
Rectal stricture	1
Enteritis	7
Anal stricture/fissure	2
Cystitis/hematuria	14
Ureteral stricture	1
Urinary incontinence	6
After transurethral resection	2/164 (1.2%)
No transurethral resection	4/413 (1%)
Urethral stricture	23
After transurethral resection	8/164 (4.9%)
No transurethral resection	15/413 (3.6%)
Scrotal/penile edema	8
Leg edema	9
After staging laparotomy	8/83 (9.6%)
No staging laparotomy	1/494 (0.2%)
Subcutaneous fibrosis	2
Scrotum, skin necrosis	1
Bladder ulcer	1
Impotence	82/210

DISCUSSION

Multiple reports have described results with radiation therapy comparable to those obtained with radical prostatectomy (14,16-19) in patients with stages A2 and B, or with hormonal manipulation in patients with stage C carcinoma of the prostate (1-4,6). Obviously, direct comparison of the various series is not possible because of patient selection, diversity of staging, pathologic classifications, and different evaluation end points. Only 1 prospectively randomized study has been published (20) on 97 patients with operable carcinoma of the prostate (stage A2 or B), with better survival noted at 5 years in the patients treated with radical prostatectomy. Unfortunately, this study has limited patient accrual and no prospective stratification for degree of differentiation of the tumor or stage; for unknown reasons, the number of patients in the surgical group is only 41 with 56 in the radiotherapy arm. The follow-up was short (5 yr) and the data have not been available for independent review. Finally, 11 of the failures in the radiation therapy group were described as abnormal bone scans and 3 as progressive elevation of acid phosphatase only, both of which are unrelated to local-regional treatment.

In a recent article, Pilepich et al. (21) compared the results of researchers at several institutions on patients treated with external-beam irradiation that were comparable to those included by Paulson in his study; the survival obtained with irradiation is similar to that reported with radical prostatectomy.

Furthermore, the 5- and 10-year survival observed after definitive irradiation is higher than that reported by Thompson (22) and Hanash et al. (23) with transurethral resection alone in patients with probably more advanced tumors. Hanash et al. (23) reviewed the data on 200 patients with histologically proven carcinoma of the prostate treated with transurethral resection of the prostate only between 1934 and 1942 (probably the same population studied by Thompson).

Patients were not clinically staged. In those with clinically latent (occult) tumors, the 5-year survival was about 50%, and the 10-year survival for all histologic grades was 30%. This was similar to the expected survival for a comparable normal population. In contrast, patients with clinically manifest tumors had a 5-year survival of 20% for grades I, II, and III and less than 5% for grade IV. The 10-year survival was less than 10% for all grades, significantly below the expected normal survival (about 40%).

The 5-year survival of 75% for patients with stage B and 58% for stage C tumors after definitive irradiation is comparable to rates reported by the Veterans Administration Cooperative Urological Research Group with prostatectomy in the first group and hormonal manipulation in the second (20,24).

Thus it appears that radiation therapy is a reasonable therapeutic alternative for patients with localized carcinoma of the prostate. Irradiation has been noted to yield control of the prostate tumor in approximately 85%-90% of the patients with stages A2 and B tumors and in 70%-75% of those with stage C lesions (1-3). Our figures are slightly lower than those reported by others, probably because of the longer follow-up on our patients; yet, they are comparable to those reported by Bagshaw and co-workers (1) in the Stanford experience.

We have noted that patients in whom control of the tumor in the pelvis is observed have a lower probability of developing distant metastases and better survival. Whether this represents a better immune response of the patient or proliferating characteristics of the tumor cannot be elucidated from our data. Furthermore, it is possible that pelvic failures antecede distant dissemination in a small proportion of the patients. Nevertheless, in our experience, pelvic tumor control is a critical parameter affecting the prognosis of these patients.

The doses of irradiation given to patients in stage B did not significantly correlate with probability of tumor control in the pelvis. However in stage C, higher doses of irradiation to the prostate resulted in better pelvic tumor control. Hanks et al. (25) reported a better 4-year, recurrence-free survival in 574 patients with various stages of carcinoma of the prostate treated with doses over 6,500 cGy. In general, these dose levels are accepted as optimal because, as noted by Hanks and associates (2) in the Patterns of Care Study analyses of patients treated with irradiation for carcinoma of the prostate, the major complication rate was 3.5% with doses below 7,000 cGy in comparison with 7% with higher doses. These observations coincide with those reported by us (26) in carcinoma of the uterine cervix, in which doses above 7,500-8,000 cGy even to small volumes were associated with a significantly greater incidence of treatment sequelae in the bladder or the rectum. The volume of tissue to be treated, as outlined by Pilepich and associates (27), is imperative to achieve optimal tumor control.

In the present series, we did not observe a significant correlation between the sequelae of therapy and doses of irradiation given. The development of sexual impotence is a disturbing and vexing sequela of therapy that greatly affects the quality of life of those patients who were potent at the time irradiation was initiated. We (28) performed serial plasma testosterone and dihydrotestosterone determinations before and after radiation therapy without significant

changes noted. Other possible causes of this undesirable sequela, such as vascular injury impairing the blood flow to the corpora cavernosa, radiation injury to the neurovascular autonomic branches governing erection, or psychologic factors, need to be elucidated further in carefully conducted prospective studies (29,30).

Previous reports have shown that concomitant administration of hormonal therapy with irradiation did not significantly affect survival or patterns of failure in these patients (14,31,32). Our analyses confirm this observation, and we reaffirm our recommendation to treat patients with localized carcinoma of the prostate with definitive radiotherapy alone, reserving hormonal manipulation for those who subsequently develop a pelvic tumor recurrence or distant metastases. This concept does not conflict with an approach suggested by Green et al. (33) and Pilepich (personal communication), who advocate a short course of hormonal therapy (3 mo) before irradiation to decrease the volume of the tumor and improve sensitivity of the neoplastic cells to irradiation. Paulson and co-workers (34) reported on a randomized study in which radiation to the pelvis was compared with delayed hormonal manipulation in 73 patients with stage C tumors. Although the recurrence-free survival was initially higher for the patients treated with irradiation, survival was comparable at 3 years, mostly because of the development of distant metastases. However, longer follow-up was not offered, and the patients' quality of life was not assessed.

CONCLUSIONS

Obviously, the need is great for more biologic research leading to a better understanding of the natural history of prostate carcinoma and the response of cells to various therapeutic agents, methods for early detection, more accurate staging, and more sensitive procedures to detect early recurrences on follow-up.

Furthermore, clinical urologists and oncologists have a critical need for standardized pretreatment evaluation criteria, staging system, pathologic classification, and statistical methodology for the analyses of therapeutic outcomes.

Ideally, patients should be evaluated conjointly by urologists and radiation oncologists, and they should be presented with explanations of the therapeutic alternatives (effectiveness, morbidity, costs), so that they can participate intelligently in the selection of their therapy. We strongly recommend properly designed and prospectively randomized studies to resolve existing controversies in the management of these patients, particularly the use of prostatectomy (radical or nerve-sparing retropubic procedures) or irradiation of stages A2 and B lesions.

The potential, albeit limited, benefit of pelvic irradiation in patients with metastatic pelvic lymph nodes deserves further evaluation.

Because of the high incidence of distant metastases, particularly in patients with stage C tumors, and the high death rate in patients with pelvic failure, it is important that we continue to search for effective cytotoxic therapy to control micro-metastases or overt clinical metastases.

In summary, in our experience, definitive radiation therapy has been shown to be an effective therapeutic modality in localized carcinoma of the prostate, with results similar to those reported in surgical series. Biologic or technical factors

that affect tumor control and prognosis should be clearly identified and, whenever required, the techniques of treatment should be modified to enhance therapeutic results.

A continued dialogue between the various specialists involved in the management of patients with carcinoma of the prostate is critical if optimal multidisciplinary care is to be fostered.

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Local Control of Prostate Cancer With Radiotherapy: Frequency and Prognostic Significance of Positive Results of Postirradiation Prostate Biopsy

Peter T. Scardino,^{1,*} Thomas M. Wheeler²

ABSTRACT—The best available data indicate that, although it is imperfect, the postirradiation biopsy performed at a sufficient interval after radiotherapy can provide accurate prognostic information useful in the determination of the success or failure of radiotherapy in an individual patient as well as the measurement of overall efficacy of any particular radiotherapeutic regimen. Needle biopsy of the prostate was performed routinely in 510 patients with clinical stage A2, B, or C1 prostate cancer treated with a combination of radioactive gold seed implantation and external-beam irradiation. Of the 140 patients who had one or more needle biopsies performed 6–36 months after completion of radiotherapy, who had no evidence of local recurrence or distant metastases at the time of biopsy, and who had received no hormonal therapy before documented recurrence of the tumor, 45 (32%) had one or more biopsies positive for cancer. The frequency of positive biopsy results correlated significantly with the size of the local tumor but not with the grade. The correlation between biopsy results and the eventual development of recurrence was highly significant. If any biopsy was positive, 60% of the patients eventually developed local recurrence; if all biopsies were negative, only 19% developed local recurrence during the period of follow-up. The poor prognosis associated with a positive biopsy result was found within almost every subset of stage, grade, or nodal status examined, although the results varied because of the small number of patients in some groups.—NCI Monogr 7:95–103, 1988.

Despite numerous reports of the use of radiotherapy to treat localized prostate cancer, there remains no consensus as to how the efficacy of radiotherapy should be measured. Various end points have been used, such as the survival rate, the disease-free survival rate, and the time to development of distant metastases. Because radiotherapy, like surgery, is a form of local or regional therapy, the best result that can be expected is complete eradication of tumor within the treated field. Consequently, the most direct measure of the efficacy of radiotherapy is the rate of local treatment failure, and the only unequivocal proof of local treatment failure is progressive growth of the primary tumor.

In any series of patients treated with radiotherapy for localized prostate cancer, the actual incidence of local treatment failure is difficult for one to identify and tends to be obscured

by the long natural history of the disease, the shortened life expectancy of the patients, and the effects of other treatments so often used, especially hormonal therapy (fig. 1). Because of these factors, investigators have sought other, more immediate, measures of the ability of radiotherapy to eradicate the local tumor, such as palpation (digital rectal examination), which is notoriously subjective (1), and postirradiation biopsy of the prostate, which remains controversial.

In this review, we will outline the problems of accurately assessing the local treatment failure rate after radiotherapy, describe our results of postirradiation needle biopsy of the prostate after a combination of gold seed implantation and external-beam irradiation, and summarize previous reports of the prognostic value of postirradiation biopsy results, demonstrating that, though it is imperfect, the postirradiation biopsy performed at a sufficient interval after radiotherapy provides accurate prognostic information that can be used to determine the success or failure of radiotherapy in an individual patient as well as the overall efficacy of any particular radiotherapeutic regimen.

BACKGROUND

Disease

Progressive growth of the primary tumor (local recurrence) after radiotherapy is best defined as a morbid clinical phenomenon manifested, e.g., by obstruction of the bladder outlet or ureter, and proved by biopsy. Local recurrence may not become apparent for many years. Even untreated localized prostate cancer has a long natural history [(2); Thorsen BJ, Fritjoffsen A: Personal communication]. Treatment with radiotherapy or hormonal therapy may delay the appearance of local recurrence even further (3–5). In patients treated with gold seed implantation and external-beam radiotherapy at hospitals affiliated with the Baylor College of Medicine, local treatment failure developed progressively up to 12 years after therapy (fig. 2). Consequently, the local failure rate reported in a given series depends heavily on the length of patient follow-up.

Clinical staging of patients with localized prostate cancer is inaccurate. Understaging occurs far more frequently than overstaging. Many patients with apparently localized tumors have unsuspected pelvic lymph node metastases or distant metastases at the time of treatment that will shorten their lives and alter their treatment programs when hormonal therapy is introduced to control symptomatic metastases. These patients will not be eligible to manifest local recurrence. In a calculation of the local recurrence rate, they would

¹ Scott Department of Urology, Baylor College of Medicine; Urology Services of The Methodist Hospital and St. Luke's Episcopal Hospital, Houston, TX.

² Scott Department of Urology, Baylor College of Medicine; Department of Pathology, The Methodist Hospital, Houston, TX.

* Reprint requests to: Peter T. Scardino, M.D., Scott Department of Urology, Baylor College of Medicine, Suite 1003, 6560 Fannin St., Houston, TX 77030.

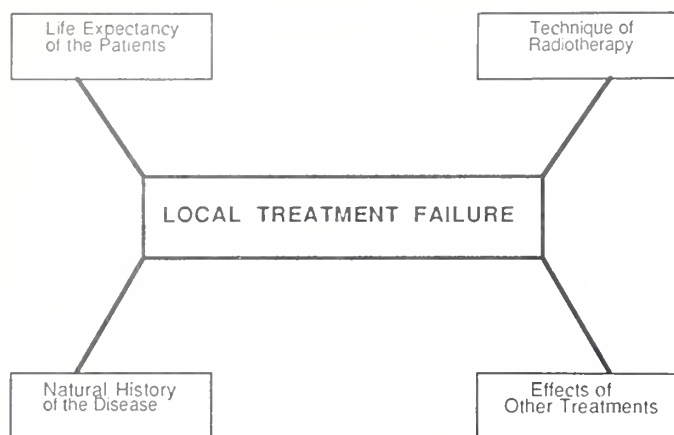


FIGURE 1.—Four major factors influencing apparent rate of local treatment failure after radiotherapy (see text).

remain part of the denominator, but they would not become part of the numerator.

Patients

Because prostate cancer is a disease of older men, who have a high incidence of comorbid conditions, many patients who present with clinically localized prostate cancer will die of other causes before the appearance of signs or symptoms of local recurrence. In our 510 patients with clinically localized prostate cancer treated with radiotherapy, the mean age was 64 years (6). These patients had follow-up for an average of 8.6 years; 22% died of prostate cancer and 21% died of other causes (table 1).

Hormonal Therapy

When hormonal therapy (androgen ablation) is used in addition to radiotherapy, the effect on the primary tumor is profound. This is a phenomenon witnessed by every urologist who administers hormone therapy to patients with metastatic prostate cancer. Often the nodular malignant prostate becomes palpably normal within several months. The degree and rate of shrinkage have been precisely documented by ultrasonography (7). Several investigators have examined the results of biopsy of the prostate after hormonal therapy alone

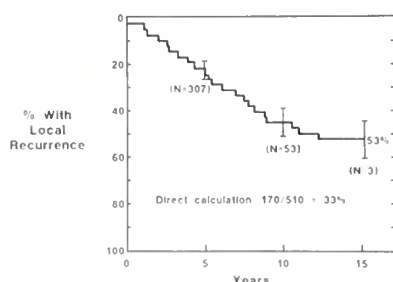


FIGURE 2.—Actuarial rate of local treatment failure in Baylor series of 510 patients treated with gold seed implantation and external-beam irradiation. At 15 yr, the *actuarial* rate of local recurrence was 53%. If direct calculation had been used, eventual risk of local treatment failure would have been substantially underestimated because 170 (33%) of 510 patients followed for a mean of 8.6 yr developed local recurrence.

TABLE 1.—Cancer status and vital status by clinical stage

Clinical stage	No. of patients	Positive nodes, %	Any recurrence, %	Percent dead of:	
				Prostate cancer	Other causes
A2 + B	393	25	42	17	21
C1	117	44	74	39	18
Total	510	30	49	22	21

for patients with locally extensive or metastatic prostate cancer and have reported that the biopsy will be converted to negative in 36%–47% of the patients (3,4).

The concomitant use of hormonal therapy will profoundly alter the incidence and apparent significance of positive post-irradiation biopsy results after radiotherapy as well as the rate of apparent local recurrence.

POSTIRRADIATION BIOPSY RESULTS

Patient Population

To evaluate the frequency and prognostic significance of positive biopsy results after definitive irradiation, we reviewed the results of routine needle biopsy of the prostate in our patients with clinical stage A2, B, or C1 prostate cancer (table 2) treated between 1966 and 1979 with a combination of radioactive gold seed implantation and external-beam irradiation (5,8–10). All 510 patients underwent staging pelvic lymph node dissection so that we could determine the dose and fields of irradiation to be used (table 3). The calculated dose of radiation to the prostate averaged $6,927 \pm 842$ (SD) cGy by the combined technique (table 4) (8,9). The clinical stage and nodal status of all 510 patients are listed in table 5.

Following treatment, prostatic tissue was obtained by needle biopsy or transurethral resection from 263 patients. To determine the prognostic significance of the identification of malignant glands in a routine needle biopsy of the prostate, we selected for analysis only those patients who had had one or more needle biopsies performed 6–36 months after the completion of radiotherapy, who had no evidence of local recurrence or distant metastases at the time of biopsy, and who received no hormonal therapy before documented recurrence of tumor. A total of 170 biopsies were performed

TABLE 2.—Staging system for prostate cancer

Stage	Disease characteristics
A1	No tumor palpable; ≤ 3 microscopic foci of well-differentiated tumor
A2	No tumor palpable; > 3 foci and/or tumor less than well differentiated
B1N	Tumor ≤ 1.5 cm; confined to one lobe
B1	Intracapsular tumor > 1.5 cm; confined to one lobe
B2	Tumor involving both lobes; confined to prostate
C1	Tumor extending beyond capsule, with or without invasion of lateral sulci or seminal vesicles; ≤ 6 cm in maximum diameter
C2	Same criteria as stage C1 disease except tumor > 6 cm

TABLE 3.—Protocol of combined gold seed implantation and external-beam radiotherapy for patients with no evidence of metastases

Pelvic lymph nodes	Gold seed implantation, cGy		External-beam radiotherapy, cGy ^a		Total dose, cGy	
	1966-1979	After 1979	1966-1979	After 1979	1966-1979	After 1979
Negative	2,500-3,000	3,500	4,000	4,500	7,000	8,000
Positive	2,500-3,000	3,500	5,000	5,400	8,000	8,900

^a Radiotherapy to prostate was given 18-21 days after gold seed implantation.

among the 140 patients who met these criteria. The clinical stage, nodal status, and grade of tumors in these patients were not significantly different from those in the remaining 370 patients, except that fewer (25%) had positive lymph nodes.

The biopsy specimens were reviewed by a single pathologist and were considered positive if any neoplastic glands were seen (fig. 3), regardless of the presumed viability of the cells or the extent of changes due to radiation (11).

End Points

For this analysis, the end point used was time to local treatment failure. Local treatment failure (local recurrence) was defined as a clinical phenomenon causing discrete signs or symptoms, such as hematuria, pelvic pain, ureteral obstruction, bladder outlet obstruction, or a progressively enlarging palpable mass. In each case, these signs or symptoms were confirmed by a tissue diagnosis of persistent prostate cancer. Neither a positive biopsy nor an abnormal digital rectal examination of the prostate was considered evidence of local treatment failure.

Results

Of the 140 patients, 45 (32%) had one or more biopsies positive for cancer (table 6). The frequency of positive biopsy results correlated significantly with the size (stage) of the local tumor; the larger the tumor was, the greater the frequency of positive biopsies, but biopsy results did not correlate with the grade of the tumor (table 7), perhaps because poorly differentiated tumors, although generally larger, may be more radiosensitive.

The correlation between biopsy results and the eventual development of local recurrence (or of any recurrence, local or distant) was highly significant (table 8). If any biopsy was positive, 60% of the patients eventually developed local recurrence; if all biopsies were negative, only 19% developed local recurrence during the period of follow-up. When the results were analyzed according to the actuarial life-table

method (fig. 4), the probability of local recurrence for patients with a positive biopsy was 52% at 5 years and 72% at 10 years; for those with a negative biopsy, it was only 12% at 5 years and 30% at 10 years ($P < .0001$).

The poor prognosis associated with a positive biopsy result was found in almost every subset of stage, grade, or nodal status examined, although the results varied because of the small numbers of patients in some groups. Of 105 patients with proven negative lymph nodes (table 9), 27 (26%) had one or more positive biopsy results after irradiation, and 50% of these patients have developed local treatment failure. Among patients carefully matched for the features of localized prostate cancer known to have prognostic importance (stage, grade, nodal status), biopsy results still retained their prognostic significance (table 10).

For example, we analyzed the results among 47 patients with a small palpable tumor confined to one lobe of the prostate (stages B1N and B1) with proven negative pelvic lymph nodes. Within this subset of patients, the risk of local recurrence was significantly greater for those with a positive biopsy (fig. 5). Of these patients, 57% developed local recurrence at 5 years, compared with only 8% if the biopsy was negative ($P < .02$).

Biopsy results correlated significantly with the results of the digital rectal examination at the time of biopsy (table 11), but even among patients with a normal digital rectal examination of the prostate, the risk of local treatment failure was significantly greater if the biopsy was positive. At 5 years, 40% of those with a positive biopsy had developed local recurrence, compared with only 7% of those with a negative biopsy (fig. 6).

Finally, we tested the hypothesis that a patient with a positive biopsy result 1 year after radiotherapy that was converted to negative at 2 years has the same favorable prognosis as a patient whose initial (1 yr) biopsy result was negative. In our series, 26 patients with a positive biopsy result 1 year after radiotherapy received no subsequent treatment but underwent a second needle biopsy approxi-

TABLE 4.—Characteristics of 510 patients and type and dose of radiotherapy

Characteristic	Mean	Range
Age, yr	64	43-82
Follow-up, yr	8.6	2.5-17.1
Mean dose of radiation, cGy		
Gold seeds	2,602	500-6,000
External-beam	4,325	3,000-5,000
Total dose, cGy	6,927 ± 842 (SD)	4,500-10,500

TABLE 5.—Clinical stage and lymph node status

Clinical stage	Patients		Percent with positive nodes
	No.	Percent	
A2	130	25	22
B1N	25	5	8
B1	140	28	24
B2	98	19	37
C1	117	23	44
Total	510	100	30

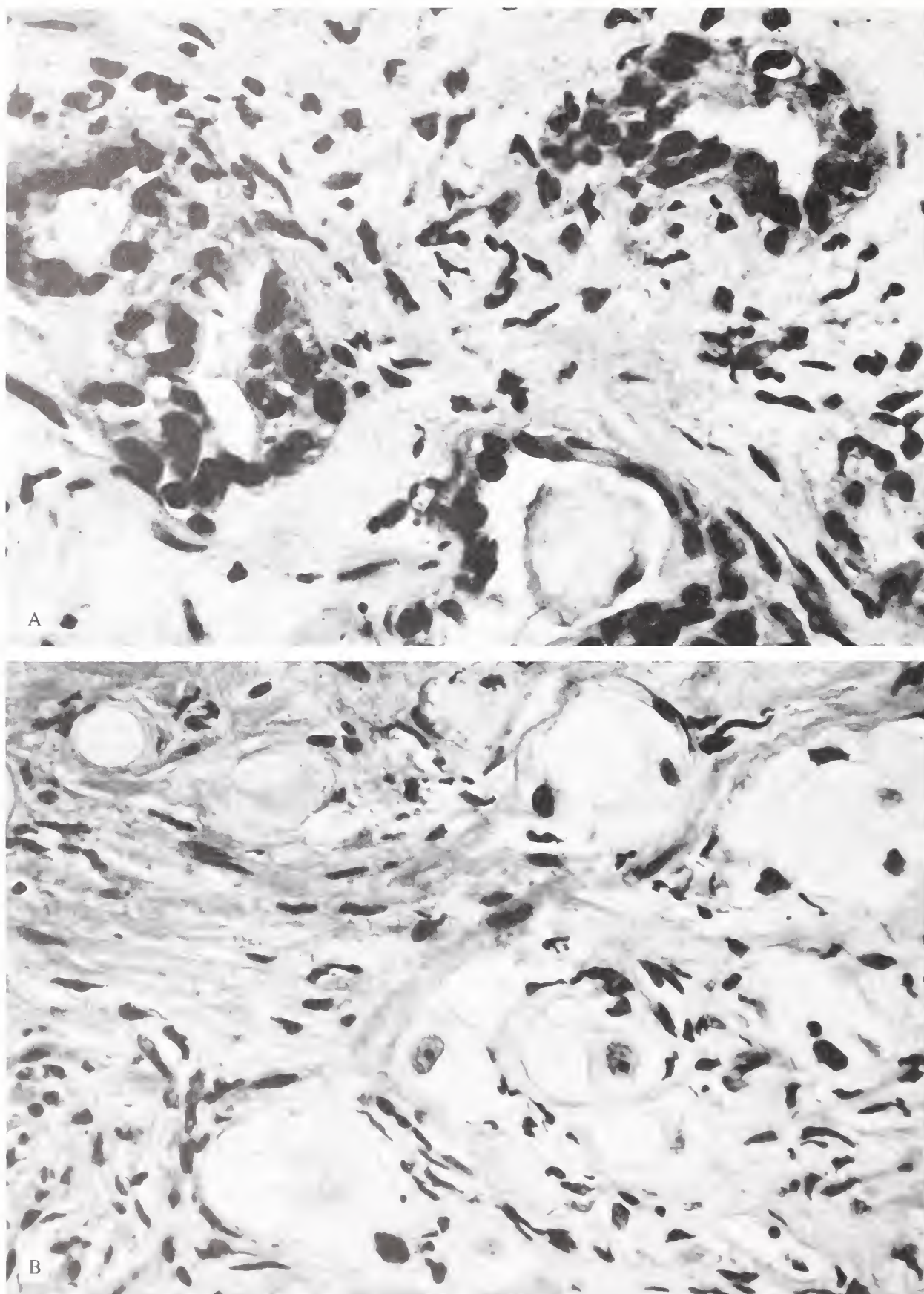


FIGURE 3.—High-power photomicrographs ($\times 315$) of radiation atypia (A) and persistent carcinoma (B).

TABLE 6.—Biopsy results by clinical stage^a

Clinical stage	No. of patients	Percent with positive biopsy
A2	22	36
B1N	9	11
B1	47	19
B2	25	32
C1	37	51
Total	140	32

^a $P < .01$ TABLE 7.—Biopsy results by grade^a

Grade	No. of patients	Percent with positive biopsy
I	53	28
II	43	35
III	28	36

^a I = well-differentiated tumor cells; II = moderately differentiated; III = poorly differentiated. Grade was not known for 16 patients. P was not significant.

TABLE 8.—Prognostic significance of prostate biopsy in 140 patients^a

Biopsy results	Patients		Recurrence, %	
	No.	Percent	Local	Any
Negative	95	68	19	35
Positive	45	32	60	76

^a $P < .0001$.TABLE 9.—Biopsy results by stage for patients with negative lymph nodes^a

Stage	No. of patients	Percent with positive biopsy
A2	17	29
B1N	8	13
B1	39	15
B2	19	26
C1	22	45
Total	105	26

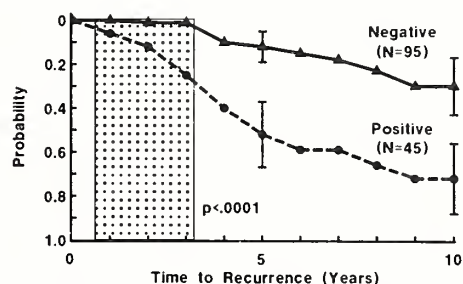
^a $P < .02$.

FIGURE 4.—Actuarial analysis showing that probability of clinical local recurrence was significantly greater if result of routine needle biopsy performed 6–36 mo (shaded area) after completion of therapy was positive for cancer.

TABLE 10.—Prediction of local recurrence by biopsy results within each stage in patients with negative lymph nodes

Clinical stage	Total No. of patients	Local recurrence				<i>P</i> ^a
		Negative biopsy		Positive biopsy		
		No. of patients	Percent	No. of patients	Percent	
A2	17	12	0	5	60	.003
B1N	8	7	29	1	0	NS
B1	39	33	12	6	67	.002
B2	19	14	20	5	0	NS
C1	22	12	25	10	70	.08
Total	105	78	15	27	52	.0001

^a NS = not significant.TABLE 11.—Correlation of patients' biopsy results with rectal examination at time of biopsy^a

Prostate examination	Patients		Biopsy results		No.	Percent
	No.	Percent	Negative	Positive		
Normal	101	72	81	20	20	20
Abnormal	39	28	14	25	64	64
Total	140	100	95	45	32	32

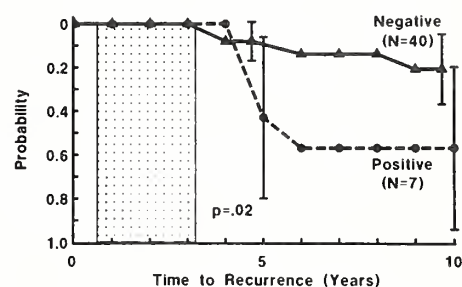
^a $P < .0001$.

FIGURE 5.—Among patients carefully matched for volume of tumor (stage B1, negative nodes), positive biopsy result 6–36 mo (shaded area) after therapy was associated with significantly greater risk of eventual local recurrence.

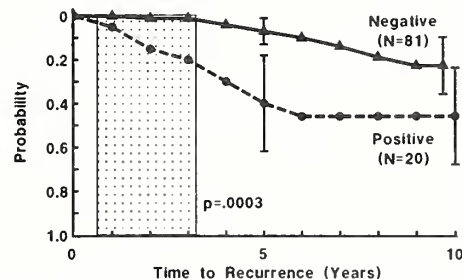


FIGURE 6.—Among patients with normal digital rectal examination of prostate at time of biopsy, positive biopsy result was associated with significantly greater risk of local recurrence.

TABLE 12.—Prognostic significance of 2nd biopsy result in patients with 1st biopsy positive

Second biopsy result	Patients		Recurrence					
			Local		Distant		Any ^a	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Negative	8	31	4	50	1	13	4	50
Positive	18	69	9	50	5	28	12	67

^a Any recurrence refers to local, or distant, or both.

mately 1 year later. In 8 of these patients, the biopsy was converted to negative, but in 18, the result remained positive. However, the risk of subsequent local treatment failure was identical (50%) in these 2 groups (table 12), which indicated that if *any* biopsy was positive in the 6- to 36-month interval, the prognosis was significantly worse, regardless of subsequent biopsy results.

DISCUSSION

The value of postirradiation biopsy results as a measure of local treatment failure has been one of the most controversial topics in urologic oncology. The issues involved are important and have direct clinical relevance. If postirradiation biopsy results are reliable, they offer an objective way for physicians to determine the efficacy of a particular radiotherapeutic regimen without waiting 10–15 years and, thereby, to eliminate the confounding effects of death from other causes or from metastatic prostate cancer and the frequent introduction of hormonal therapy. In our experience (12), the results of postirradiation biopsy performed at a sufficient interval after radiotherapy correlate significantly with the ultimate outcome of therapy.

Since we published our initial report (12), our conclusions have been criticized on the basis that the patients selected for biopsy were not representative of the entire group treated. In fact, we have not been able to find any significant differences in the stage, grade, nodal status, risk of recurrence (either local or distant), or survival rates between the 140 patients who had biopsies and the 370 who did not (fig. 7). Several unselected series in which every patient underwent biopsy have reported results similar to ours (13–15).

Other investigators (16) have questioned the quality of the particular radiotherapeutic regimen that we used, but the long-term survival rates of our patients are virtually identical to those reported after external-beam irradiation (table 13). Among patients with carefully staged disease who had proven negative pelvic lymph nodes and were treated with external-beam irradiation alone (16) or with combined gold seed implantation and external-beam radiation therapy (our studies), there were no differences in time to appearance of distant metastases or cancer-specific survival rate (fig. 8). In fact, a comparison of postirradiation biopsy results in our patients with those reported from Stanford University Medical Center (16,17) indicates that, on a stage-for-stage basis, positive biopsy results after irradiation were less frequent in our series (table 14).

Certainly the meaning of a positive biopsy result after irradiation will depend on the quality of the radiotherapeutic

technique used. If few patients ever developed local recurrence, routine needle biopsies after irradiation would be irrelevant. To date, however, local treatment failure has been a problem in every series in which it has been carefully analyzed and in which the confounding effects of hormonal therapy, death from other causes, and death from prostate cancer have been eliminated.

A number of concerns have been raised about the interpretation of postirradiation needle biopsies. A biopsy often provides only a random sample of the prostate, especially in patients who have no palpable nodule to be used as a target, and may therefore miss foci of residual tumor, a problem that may be alleviated with the advent of ultrasonically guided biopsy of the prostate.

A second concern is the difficulty with histologic interpretation of biopsy specimens; radiation-induced atypia may be confused with residual carcinoma in the irradiated prostate (fig. 3). In particular, Cox and Stoffel (18) and Cox and Kline (19) have questioned the interpretation of postirradiation biopsy, strongly arguing the impossibility of distinguishing viable from nonviable, lethally irradiated cells on histologic grounds, but this issue has been re-examined by Bostwick et al. (11), who have clearly defined the criteria for recognizing carcinoma in postirradiation biopsy specimens and distinguishing it from radiation-induced atypia of nonmalignant glands. They have criticized the concept of "nonviable" cancer, which indeed is not a recognized phenomenon in other human tumors, and have argued that this concept

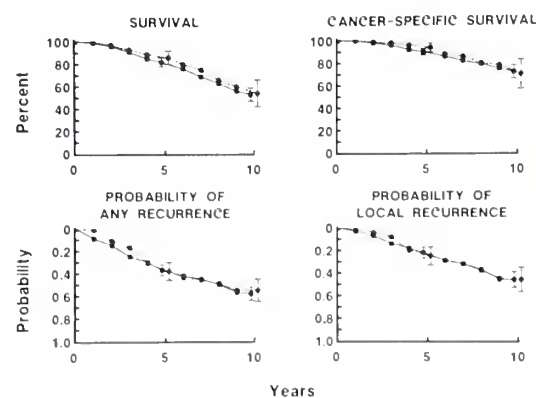


FIGURE 7.—Actuarial survival rate, cancer-specific survival rate, probability of any recurrence (local or distant), and probability of local recurrence among patients treated with gold seed implantation and external-beam radiotherapy. Comparison of 140 patients who had a postirradiation needle biopsy (closed circles) of prostate with 379 patients who had no needle biopsy (closed squares) shows no differences between groups.

TABLE 13.—Comparison of actuarial survival rates after external-beam radiotherapy and combined gold seed implantation plus external-beam radiotherapy

Clinical stage	Technique	No. of patients	Actuarial survival rates, % ^a		
			5 yr	10 yr	15 yr
A2 + B	External ^b	491	81 ± 4	60 ± 5	34 ± 6
	Combined ^c	393	86 ± 4	59 ± 6	28 ± 13
C	External ^b	407	61 ± 5	35 ± 5	17 ± 5
	Combined ^c	117	74 ± 8	34 ± 12	17 ± 13

^a Values are means ± 2 SE; 95% confidence intervals.

^b See (16).

^c Data are from our present study.

should no longer be applied to postirradiation biopsy of the prostate.

A third major concern is that the time after radiotherapy that a biopsy can be considered reliable has not been clearly defined. Again, Cox and Stoffel (18), who are among the strongest proponents of the hypothesis that postirradiation biopsy results have no prognostic significance, have argued to a great extent on the basis of their finding that the incidence of positive biopsies decreased with time after radiotherapy. In their series, the incidence of positive biopsies decreased from 65% at 6 months to 19% at 24 months or more. This perplexing phenomenon has often been cited as proof that a postirradiation biopsy less than 24 months after radiotherapy is unreliable. In our series, we found a similar but more rapid decline with time after radiotherapy (fig. 9), but with a plateau by 12 months at a level of about 35% positive biopsies (5). There are several problems with the analysis of Cox and Stoffel; the most damaging to their conclusion is that nearly one-half of their patients received hormonal therapy. Their patients were seen and followed regularly by the urologists at the Walter Reed Army Medical Center, who administered hormonal therapy to many patients before and after radiotherapy. Consequently, we cannot attribute the decreasing

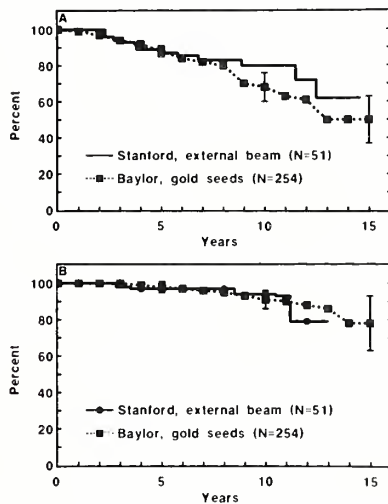


FIGURE 8.—Comparison of time to distant metastases (A) and cancer-specific survival (B) rates among patients with carefully staged disease (stages A2 and B, negative pelvic lymph nodes) treated with external-beam radiotherapy alone (16) or combined gold seed implantation and external-beam radiotherapy (our series) during comparable years.

TABLE 14.—Postirradiation biopsy results

Clinical stage	Gold seeds plus external-beam radiotherapy ^a		External beam radiotherapy alone ^b	
	No. of patients	Percent with positive biopsy	No. of patients	Percent with positive biopsy
A2	23	35	1	0
B1N	9	11	2	0
B1	48	21	8	38
B2	27	33	22	59
C	40	55	31	74
Total	147	34	64	61

^a Data are from our present study.

^b See (17).

incidence of positive biopsies reported by Cox and Stoffel to the effects of radiotherapy alone; we must include the combined effects of radiotherapy and hormonal therapy (3,4). In our series, in which hormonal therapy was not used before documented recurrence of tumor, patients with a positive biopsy at 1 year had a poor prognosis regardless of the results of a second biopsy done 1 year later (table 12). Such late biopsies may simply miss small foci of residual carcinoma, which will eventually regrow and cause local recurrence.

Not all patients with a negative biopsy result after irradiation remain free of local treatment failure, nor do all patients with a positive biopsy develop local recurrence. There are a number of valid explanations for false-negative biopsy results. If a sampling error occurs, especially in a patient with no palpable nodule, persistent tumor not included in the specimen will eventually grow and cause local tumor recurrence. In other instances, a negative biopsy may be accurate, but the prostate is left in situ after radiotherapy, because a second primary tumor may develop and be attributed to persistence of the original tumor. Lastly, a false-negative result may be reported if persistent carcinoma is misinterpreted as radiation-induced atypia.

False-positive results can also be explained. Some patients with a positive biopsy may not develop local recurrence because of the limited time of follow-up or because of early death from metastatic prostate cancer or other causes. In other patients, metastases develop before clinical local recurrence, as we have defined it, becomes apparent. These

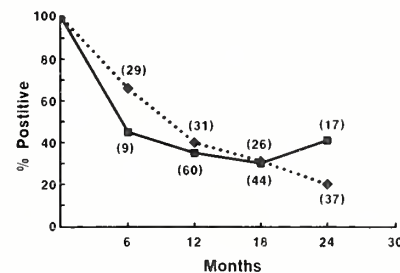


FIGURE 9.—Incidence of positive postirradiation biopsy results declined with time after radiotherapy, reaching a minimum at 12 mo in our series in which no hormonal therapy was given (closed squares), and 24 mo in the series of Cox and Stoffel (18) in which hormonal therapy was widely used (closed diamonds). Values in parentheses = numbers of patients who had biopsies at each interval.

TABLE 15.—Prognosis based on postirradiation biopsy results after various radiotherapy techniques

Technique	References	No. of patients	No. of patients							
			Negative biopsy				Positive biopsy			
			Total		Recurrence		Total		Recurrence	
			No.	Percent	No.	Percent	No.	Percent	No.	Percent
External-beam radiotherapy	13-15,17,20-22	273	126	46	18	14	147	54	75	51
Gold seed + external-beam radiotherapy	12	124	81	65	25	31	43	35	28	65
Iodine-125	23-25	109	71	65	15	21	34	35	19	56
Total		506	278	55	58	21	224	45	122	54

patients receive hormonal therapy, which may obscure the manifestation of local recurrence during the remainder of their lives. Lastly, a false-positive result may occur if radiation-induced atypia is misinterpreted as persistent carcinoma.

In a review of the literature (12-15,17,20-25), we have identified 506 patients, including those in our study, who were treated with either external-beam irradiation alone, combined gold seed implantation plus external-beam irradiation, or iodine seed implantation (table 15). Of these patients, 45% had a positive biopsy result after irradiation, and 54% of these had evidence of treatment failure at the time of the report (mean, 4 yr), compared with only 21% of the patients with a negative biopsy. Recently, Schellhammer et al. (26) reported their experience with postirradiation biopsy results after external-beam irradiation alone or iodine-125 implantation in patients who received no hormonal therapy before documented recurrence. The frequency and the prognostic significance of positive biopsy results after irradiation were similar to ours.

In summary, the best available data indicate that a physician can perform needle biopsy of the prostate at a sufficient interval after radiotherapy to determine the efficacy of a particular radiotherapeutic technique. Biopsy results offer the clinician a way to determine the success or failure of radiotherapy in the individual patient. Further efforts of physicians should be directed toward defining the earliest time after the initiation of radiotherapy that biopsy results can be considered reliable and, most importantly, identifying how patients with positive biopsy results after irradiation should be treated.

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III. Surgery

Selection Criteria for Radical Prostatectomy Based on Morphometric Studies in Prostate Carcinoma¹

Fuad S. Freiha,* John E. McNeal, Thomas A. Stamey²

ABSTRACT—Morphometric reconstruction of 122 consecutive radical prostatectomy specimens were analyzed for cancer volume and grade, seminal vesicle (SV) invasion, lymph node (LN) metastasis, and complete capsular penetration. The mean cancer volume for 91 specimens without SV invasion or LN metastasis was 3.7 cm³; for 14 with only SV invasion, 9.0 cm³; for 17 with LN metastasis, 15.2 cm³; and for 12 with both SV invasion and LN metastasis, 17.8 cm³. The mean cancer volume for 60 specimens without capsular penetration was 2.5 cm³, and for 62 it was 9.0 cm³. Grade of cancer correlated well with tumor volume. We believe that radical prostatectomy for cure should be performed on patients with tumors less than 3.8 cm³ in volume. Methods for accurate assessment of tumor volume before surgery should be given research priorities.—NCI Monogr 7:107-108, 1988.

The malignant potential and capacity of prostate carcinoma to metastasize are functions of degrees of differentiation and tumor volume (1). Prostate cancer dedifferentiates as tumor volume increases (2). Morphometric analyses of 122 consecutive radical prostatectomy specimens confirm these findings and identify tumor volumes that influence the selection of appropriate therapy for the patient with clinically localized disease.

MATERIALS AND METHODS

One hundred twenty-two consecutive radical prostatectomy specimens were studied by the step-section technique. After fixation in 37% formalin, the gland was serially sectioned at 3-mm intervals perpendicular to the rectal surface and separated into right and left halves. Sections were embedded in paraffin and cut at 7 μ m and stained with hematoxylin and eosin.

We determined cancer volume by outlining the tumor on every slide, calculating its surface area with the use of a Compaq computer, and multiplying that by the section thickness. For correction for tissue shrinkage caused by fixation, the sum total was multiplied by a factor of 1.5.

Seminal vesicle invasion and lymph node metastasis were quantitated and recorded.

Complete penetration of the capsule by cancer cells, referred to as level III capsular penetration, was quantitated and measured by linear centimeters.

The grade of cancer was determined according to the Gleason classification (3), and the percent of each histologic pattern was recorded.

RESULTS

Seventeen of the 122 specimens had lymph node metastases and 26 had seminal vesicle invasion. Twelve of the 26 with seminal vesicle invasion also had lymph node metastases. Complete capsular penetration was present in 62 specimens; 16 had less than 1 cm and 46 had more than 1 cm of linear penetration along the capsule.

The mean cancer volume for all 122 was 5.8 cm³, with a range of 0.01 to 42.10 cm³. The mean percent Gleason histologic pattern 4 and/or 5 present in all 122 specimens was 29% with a range of 0% to 100%. Tables 1 and 2 show the correlation between tumor volume and grade, seminal vesicle invasion, and lymph node metastasis, all of which were closely interrelated.

The incidence of lymph node metastasis and seminal vesicle invasion in relation to the presence or absence and extent of capsular penetration is shown in table 3.

The mean cancer volume for 60 specimens without capsular penetration was 2.5 cm³, with a range of 0.01 to 23.60 cm³. The large tumors that exhibited no capsular penetration had little or no Gleason histologic pattern 4 and/or 5. Tables 4 and 5 show the correlation between volume, grade, and capsular penetration. Of the 46 specimens with more than 1 cm of penetration, 17 had neither lymph node metastasis nor seminal vesicle invasion, and the mean cancer volume for these 17 was 7.3 cm³, a figure which remains significant when compared with the mean of those samples without capsular penetration.

DISCUSSION

Before recommending radical prostatectomy to a patient with clinically localized prostate cancer, the urologist must try to answer two questions: 1) How much cancer does the

¹ Supported by a grant from the Richard M. Lucas Cancer Foundation.

² Division of Urology, Department of Surgery, Stanford University School of Medicine, Stanford, CA.

* Reprint requests to: Fuad S. Freiha, M.D., Division of Urology, Department of Surgery, Stanford University School of Medicine, 300 Pasteur Dr., Stanford, CA 94305-5118.

TABLE 1.—Correlation between tumor volume, seminal vesicle (SV) invasion, and lymph node (LN) metastasis

Metastasis/ invasion	No. of specimens	Volume, cm ³		P
		Mean	Range	
Negative LN Negative SV	91	3.7	0.01–26.50	
Positive LN Positive SV	12	17.8	4.91–42.10	<.001
Positive LN	17	15.2	3.69–42.10	<.001
Negative LN Positive SV	14	9.0	1.33–24.40	<.001

TABLE 2.—Correlation between Gleason grade, seminal vesicle (SV) invasion, and lymph node (LN) metastasis

Metastasis/ invasion	No. of specimens	Percent Gleason grade ≥ 4		P
		Mean	Range	
Negative LN Negative SV	91	17	0–100	
Positive LN Positive SV	12	63	20–100	<.001
Positive LN	17	62	20–100	<.001
Negative LN Positive SV	14	34	0–100	<.01

patient have? 2) What is the largest cancer that may be cured by radical prostatectomy?

The urologist continues to rely on the rectal examination to answer the first question. Even to the most experienced among us, rectal examination is highly inaccurate in assessing the extent of local disease and often underestimates its volume (4). Transrectal ultrasound and magnetic resonance imaging are promising new modalities that may prove to be more accurate than the rectal examination. The use of tumor markers such as the prostate-specific antigen may also aid in the preoperative assessment of cancer volume and extent.

To answer the second question, we performed morphometric reconstructions of radical prostatectomy specimens and analyzed them for cancer volume and grade, extent of capsu-

TABLE 3.—Capsular penetration and incidence of lymph node metastasis and seminal vesicle invasion

Capsular penetration	No. of specimens	Lymph node metastasis		Seminal vesicle invasion	
		No.	Percent	No.	Percent
None	60	0	0	1	2
<1 cm	16	0	0	1	6
>1 cm	46	17	37	24	52

TABLE 4.—Correlation between tumor volume and capsular penetration

Capsular penetration	No. of specimens	Volume, cm ³		P
		Mean	Range	
None	60	2.5	0.01–23.60	
<1 cm	16	4.3	1.46–16.32	Not significant
>1 cm	46	10.6	1.47–42.10	<.001

TABLE 5.—Correlation between tumor grade and capsular penetration

Capsular penetration	No. of specimens	Percent Gleason grade ≥ 4		P
		Mean	Range	
None	60	9	0–80	
<1 cm	16	19	0–70	.05
>1 cm	46	46	5–100	<.001

lar penetration, seminal vesicle invasion, and lymph node metastasis to find the largest tumor amenable to cure by radical prostatectomy.

Analysis of these morphometric studies has identified ranges of tumor volumes that may influence selection of appropriate therapy for the patient with clinically localized disease. Patients with tumors that are less than 3.8 cm³ in volume do not have seminal vesicle invasion or lymph node metastasis and, therefore, will have an excellent chance for cure by radical prostatectomy.

Tumors with volumes between 2.6 and 3.7 cm³ exhibit complete capsular penetration. The exact significance of complete capsular penetration in the absence of seminal vesicle invasion or lymph node metastasis is not known. We now have 17 such patients who are being followed closely with examinations, prostate-specific antigen determinations, and bone scans; we hope to learn more about the significance of this pathologic finding.

Tumors with volumes up to 2.5 cm³ are localized and exhibit neither capsular penetration nor lymph node metastasis.

Now that we have identified ranges of tumor volumes with prognostic significance, the need for methods to measure preoperative tumor volume accurately becomes apparent.

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Bilateral Pelvic Lymphadenectomy and Radical Retropubic Prostatectomy for Stage C or D1 Adenocarcinoma of the Prostate: Possible Beneficial Effect of Adjuvant Treatment

Horst Zincke¹

ABSTRACT—Limited clinical stage C (T3 NX M0) disease can be treated surgically, and morbidity can be acceptable. When appropriate adjuvant therapy (orchiectomy and/or radiation) is administered, residual cancer can be controlled locally for at least a limited period. The incidence of local progression in pathologic stage C or D1 disease may be negligible after early adjuvant orchiectomy and/or radiation treatment. The combination of immediate orchiectomy and radical prostatectomy has been shown to limit progression significantly ($P = .0009$) in many patients with D1 (T0-3 N1,2 M0) disease. However, some patients do not respond to this combination treatment, which suggests that systemic dissemination of heterogeneous tumor cells is unresponsive to adjuvant androgen ablation therapy. The DNA ploidy pattern may be a valuable predictor of disease outcome after treatment in stage D1 disease. Other pathologic variables (including acid phosphatase levels) have not been useful in predicting disease outcome or treatment response. Finally, patients with limited clinical stage C disease and those with pathologic C or D1 disease should be enrolled in a prospective randomized protocol so that the possible beneficial effects of adjuvant treatment programs can be evaluated. Apart from the usual pathologic variables and prostate-specific antigen testing, the DNA ploidy pattern should be included as a stratification factor.—NCI Monogr 7:109-115, 1988.

Adenocarcinoma of the prostate is the second most frequent cause of death from cancer in the United States. For 1987, it has been projected that 96,000 new patients will have tumor of the prostate and that 27,000 will die of prostate cancer (1). Thus cancer of the prostate is not an innocuous disease. However, depending on its grade and stage at the time of presentation, the tumor can be curable.

Conceptually, only a small percentage of patients with cancer of the prostate qualify for radical prostatectomy (2). The rationale for this attitude originated from reports of small series in which survival rates were favorable only for patients with small lesions (≤ 1.5 cm, stage B1/T1) and were poor for patients with larger lesions. In most of these studies, however, accurate staging (by bone scan and pelvic lymphadenectomy) was not done. Thus many of the patients who were believed to have localized lesions had locally extended disease at surgery, and some also might have had metastatic disease. Hence the concept evolved that patients with clinical stage B2 (T2) disease (e.g., ≥ 2 cm, clinically localized to prostate, 50% of whom have pathologic local extraprostatic disease) are unsuitable surgical candidates. Conservative treatment (hormonal or radiation, or both) was recommended for these

patients. The short-term (5-10 yr) survival when irradiation is used for this stage of the disease (3-6) is similar to that achieved by radical prostatectomy without adjuvant treatment for localized cancer. However, radical prostatectomy for localized cancer preceded by bilateral pelvic lymphadenectomy recently has been preferred by an increasing number of surgeons because of the observed favorable long-term local and systemic control (7) unmatched by conservative treatment modalities and its potential as a potency-preserving procedure (8).

Many patients have neither localized nor distant metastatic cancer but have locally extracapsular disease with or without regional lymph node involvement. Treatment for these patients has been discussed with considerable controversy during recent years (9-12). This controversy involves the question whether additional treatment is needed for local stage C (pT3) disease which, before and during surgery, had been perceived as a localized lesion only, but which unexpectedly was discovered on histopathologic examination of the prostate after radical prostatectomy to be extracapsular disease with or without regional lymph node involvement. The treatment approach for primary limited clinical stage C (T3 NX M0) disease and the management for stage D1 (T0-3 N1,2 M0), i.e., regional lymph node involvement, recognized only at pelvic lymphadenectomy and usually preceding an originally planned radical prostatectomy, have been of particular concern to many investigators (9,11,13).

Surgery as a treatment option for clinical stage C disease has usually been excluded because of the historically poor results when perineal prostatectomy only was used. However, reports of physicians using this approach lacked appropriate staging (by pelvic lymphadenectomy), and the opportunity for appropriate adjuvant treatment was missed. Because of the high incidence of residual cancer after surgery for this stage of the disease and the high incidence of pelvic lymph node involvement ($>50\%$), which many consider to be a contraindication to radical surgery, radiation had been preferred to radical surgery for the treatment of clinical stage C cancer of the prostate. The problems associated with local and systemic control with this large tumor bulk and usually high-grade cancer have been recognized, and augmentation therapy has been suggested (12). Of particular concern has been the persistence and/or local recurrence of the disease after radiation that is usually associated with an ominous prognosis (14). Morbidity in patients who fail after local radiation has been high and has resulted in significant impairment in the quality of life (15). In this context, the goals of therapy for patients with clinical stage C disease should

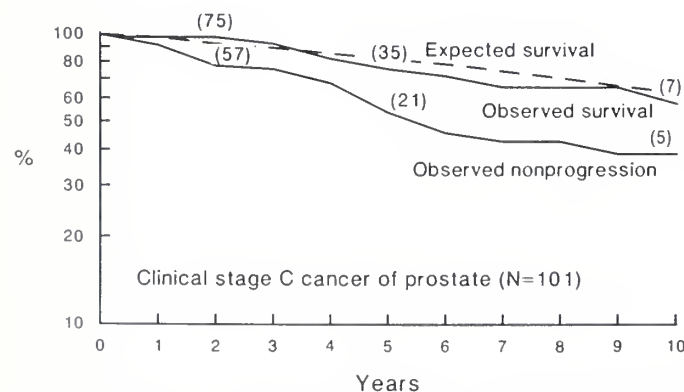
¹ Department of Urology, Mayo Clinic and Mayo Foundation, 200 First St., S.W., Rochester, MN 55905.

include not only prolongation of survival but also control of local progression with its associated decrease in complications and thus possible improvement in quality of life. Hence monotherapy for stage C disease of the prostate currently seems to be less attractive, particularly when a cancer is locally in an advanced clinical and pathologic stage.

Patients with limited but unequivocal clinical stage C cancer of the prostate (without involvement of bladder base at cystoscopy) can be treated successfully with bilateral pelvic lymphadenectomy, radical prostatectomy, and adjuvant treatment without significant morbidity and with excellent long-term results in nonprogression and survival (9,16).

TREATMENT OF CLINICAL STAGE C ADENOCARCINOMA OF THE PROSTATE

A previous report (9) involved 101 patients with a mean age of 64 years (range, 40–74 yr) who had limited but unequivocal clinical stage C (T3 NX M0) adenocarcinoma of the prostate on clinical examination. These patients underwent bilateral pelvic lymphadenectomy and radical prostatectomy. Patients had clinical stage C disease based on digital rectal examinations and no evidence of metastasis, as determined by radionuclide bone scanning and roentgenograms as well as by laboratory tests, including measurements of total and tartrate-inhibited fractions of acid phosphatase. Follow-up ranged from 0.5 to 17 years (mean, 4.9 yr). Fifty patients were followed for a minimum of 5 years and 10 were followed for 10 years. Of these patients, 35 were under observation at 5 years and 7 were under observation at 10 years. At these respective intervals, 21 and 5 were free of disease. Regular follow-up included quarterly examinations during the first postoperative year, biannually during the second year, and usually annually thereafter if the disease had not progressed. In addition to the usual tests, a bone scan was performed at least twice annually during the first 2 years and annually thereafter. Disease progression was judged to be present if there was biopsy-proven local recurrence or if



Figures: Numbers in parentheses represent numbers of patients under observation at that time.

FIGURE 1.—Survival curves of 101 patients with clinical stage C adenocarcinoma of prostate. Curves of expected survival, overall survival, and observed nonprogression are shown. Expected survival is based on 1970 United States life tables for North Central United States. Modified from Zincke et al. (9). Reproduced with permission of the publisher.

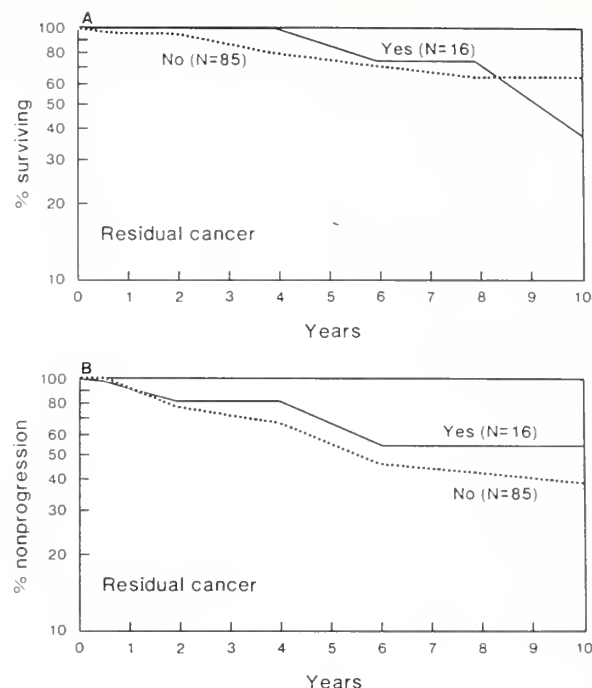


FIGURE 2.—Residual cancer and survival (A) and nonprogression (B) in 101 patients with prostate cancer. Reproduced with permission of the publisher (9).

radionuclide bone scans or roentgenograms (or both) became positive. An abnormal acid phosphatase level alone was not considered to be consistent with metastasis.

Analyses of local, systemic, and overall progression as well as overall survival and survival according to cause-specific death were always performed according to the grade and extent of the tumor (measured in cubic centimeters, seminal vesicle involvement) and whether margin-positive disease (residual cancer) was histopathologically identified at radical prostatectomy and was left behind. We attempted to remove all residual tumor. However, removal was not possible in all patients, and tumor was left behind rather than risking intentional incontinence. Lymph node involvement was quantified.

Of the 101 patients, 52 had positive lymph nodes. One-third of these 52 did not receive adjuvant treatment, whereas almost two-thirds of the patients who had pathologic stage C lesions received no adjuvant treatment. The most frequently administered adjuvant treatment was orchiectomy with or without additional treatment (30 and 12 patients with pathologic stage D1 and C lesions, respectively). Statistical analysis was done by the Kaplan-Meier method, and regression analysis was performed according to the Cox proportional hazards model. The observed survival of the 101 patients was similar to the expected survival of an age- and sex-matched control group of the general population of the North Central United States (fig. 1). Absence of cure is demonstrated in the continuously declining observed nonprogression curve. Nonprogression and survival curves were similar for stages C and D1 disease. Residual cancer was present in 16 patients and did not affect survival and nonprogression significantly (fig. 2). Patients who had undergone either orchiectomy or irradiation had no evidence of

local recurrence during follow-up. Conversely, none of the 16 patients with local recurrence had evidence of residual cancer, and 13 of the 16 had not received adjuvant treatment (table 1). Of 47 patients who received no adjuvant treatment, 13 (28%) had local recurrence. None of the 48 patients who had received adjuvant radiation and/or orchiectomy with or without additional diethylstilbestrol had a local recurrence, but 3 of 6 patients treated with diethylstilbestrol did. Local recurrence seemed to be related to tumor grade but not to number of involved nodes. Residual disease was not associated with local recurrence because these patients had received adjuvant treatment. Specifically, adjuvant orchiectomy was not associated with local recurrence.

Of the 52 patients who had positive pelvic lymph nodes, 30 underwent immediate adjuvant orchiectomy (91% were disease-free at 5 yr), which significantly delayed progression, compared with the 22 patients who did not have immediate orchiectomy (11% were disease-free at 5 yr; $P < .0001$; fig. 3A). Adjuvant orchiectomy resulted in a 5-year survival of 91%, compared with 58% ($P = .09$) when it was not used (fig. 3B).

In a more recent analysis of 384 patients who had pathologic stage C disease (pT3 N0 M0), 70 originally had clinical stage C disease (18%); the mean age of this group was 64 years. The mean follow-up was 4.5 years, with a median of 3.6 years and a range of 1 to 18 years. Of the 384 patients, 326 are still alive and are being followed. Thirty patients (8%) have died of prostate cancer. As in previous experience, 5- and 10-year survival rates (87% and 67%, respectively) were similar to the expected survival (83% and 64%, respectively; fig. 4). Analysis for cause-specific deaths only revealed a 5- and 10-year survival of 94% and 81%, respectively (fig. 5). The continuously declining curve (the last patient

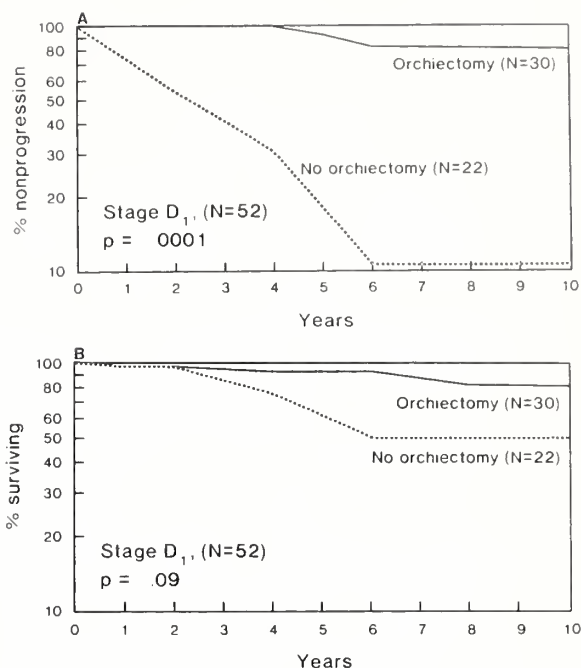


FIGURE 3.—Adjuvant treatment and nonprogression (A) and survival (B) in 52 patients with pathologic stage D1 prostate cancer. Reproduced with permission of the publisher (9).

died at 13 yr after initial treatment) lends credence to the impression that cure cannot be expected in this difficult patient population. Overall nonprogression at 5 and 10 years was 71% and 52%, respectively, whereas local recurrence was absent in 85% and 71% of the patients at 5 and 10 years, respectively. Local recurrence was significantly associated with seminal vesicle involvement as well as tumor grade. In patients with grade 3 or 4 disease, local recurrence was absent at 10 years in only 67%.

Similar to a previous study, residual cancer (usually treated by adjuvant therapy) was not significantly related to systemic or local progression. Furthermore, among 280 patients who did not receive adjuvant treatment (usually having low-grade disease and no seminal vesicle involvement), overall progression occurred in 25% but in only 10.8% (4 of 37 patients) of

TABLE 1.—Data on 16 patients with local recurrence after radical surgery for clinical stage C adenocarcinoma of the prostate

Patient No.	Pathologic stage	Residual cancer	Adjuvant treatment ^a	Time to local recurrence, mo	Survival, mo
1	C ^b	No	No	26	97
2	C ^b	No	No	67	95
3	C	No	DES	16	47 ^c
4	C	No	No	12	61
5	C	No	No	25	49
6	C	No	No	81	99
7	C	No	No	30	42
8	C	No	No	52	104
9	D1	No	DES	58	202
10	D1 ^b	No	No	56	88
11	D1 ^b	No	No	13	46
12	D1 ^b	No	No	9	36 ^c
13	D1	No	No	4	66 ^d
14	D1 ^b	No	DES	18	51 ^d
15	D1 ^b	No	No	10	76
16	D1	No	No	7	48 ^c

^a DES = diethylstilbestrol.

^b Seminal vesicle involvement was observed.

^c Patient died of cancer.

^d Patient died of unrelated cause.

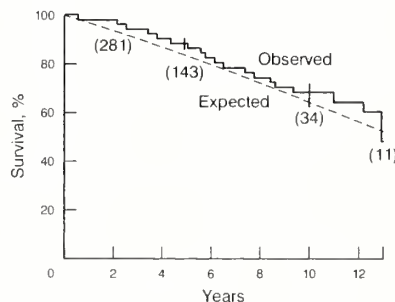


FIGURE 4.—Kaplan-Meier survival curve of 384 patients with pathologic stage C (pT3) prostate cancer who were treated with bilateral pelvic lymphadenectomy and radical retropubic prostatectomy, compared with expected survival of an age- and sex-matched control group of the North Central United States.

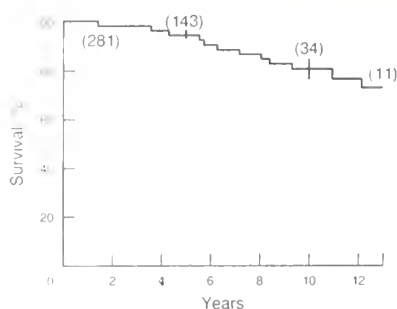


FIGURE 5.—Kaplan-Meier survival curve of 384 patients with pathologic stage C (pT3) prostate cancer who were treated with bilateral pelvic lymphadenectomy and radical prostatectomy, according to cause-specific death (prostate cancer).

those who underwent orchiectomy with or without diethylstilbestrol and/or radiation treatment (usually having high-grade disease and seminal vesicle involvement). More than 40% of the patients receiving oral hormones only had progression. Radiation alone (25 patients) and orchiectomy (37 patients) effectively reduced local recurrence (0% and 2.7%, respectively) in these patients, but 41 of the 280 patients (14.6%) without adjuvant treatment had local recurrence ($P = .02$). Furthermore, evidence from the analysis indicated that clinical stage did not affect the decision in regard to adjuvant treatment. Rather, the pathologic finding seemed to dictate the physician's decision whether to apply additional treatment.

TREATMENT OF STAGE D1 ADENOCARCINOMA OF THE PROSTATE

Reported experience of the surgical and nonsurgical management of stage D1 (pT0–3 N1,2 M0) cancer of the prostate is limited. Randomized studies for this stage have not been performed. Observation only, as shown by Paulson (11), led to progression in 50% or more of the patients at less than 2 years, and most single treatment regimens (surgical or conservative) have resulted in progression in the same percentage of patients at 5 years (17). Only recently have results of combination treatments been published by others (18,19). Of 33 patients who underwent radical prostatectomy in the series of deKernion et al. (18), 25 received adjuvant treatment in the form of radiation or hormones. The fact that only 4 of 10 patients are free of disease after radical prostatectomy and hormone and radiation therapy may reflect disease variables rather than the treatment itself, in particular because all 8 of the patients who underwent radical prostatectomy only are still alive and free of disease at follow-up of 5 years.

In a series of 27 patients with stage D1 disease who underwent radical prostatectomy, Lange and colleagues (19) administered adjuvant radiation in 21; the median follow-up period was 48 months. Recurrence was observed in 3 of the 21 patients, 2 of whom had a response to bilateral orchiectomy. These results suggest that adjuvant treatment combined with cytoreductive surgery may be beneficial in these patients, when comparison is made with patients treated by radical prostatectomy only (11). The only other large series of patients who had been treated for stage D1 prostate cancer is that involving 61 patients reported by Bagshaw (12), who

achieved 5- and 10-year survival rates of 50% and 20%, respectively, with external-beam irradiation alone. Disease-free survival was not discussed.

The generally poor results observed (11,12,17) with conservative monotherapy have led to disillusionment among many investigators, and some have advised observation only until symptomatic progression occurs. Many investigators believe that surgical treatment is inappropriate for a disease that has become systemic, albeit also larger locally.

This fatalistic view has not been shared by my colleagues and me because of our favorable early experience with combination treatment (radical prostatectomy plus immediate orchiectomy). Our initial experience in the treatment of stage D1 disease by means of bilateral pelvic lymphadenectomy and radical prostatectomy with or without adjuvant treatment was reported in 1978 (20). Since then, my colleagues and I have extended the indications to include patients with limited clinical stage C lesions (9) and some with multiple positive pelvic lymph nodes (≤ 10 nodes). We do not include patients with involved periaortic and pericaval lymph nodes, a determination that can be made at pelvic lymphadenectomy.

From 1966 to 1985, my associates and I performed pelvic lymphadenectomy and radical prostatectomy, with or without adjuvant treatment, on 1,473 patients who had all stages of prostate cancer. Of these, 195 patients (13%) had stage D1 disease (fig. 6). The ages of the 195 patients ranged from 40 to 77 years (mean, 64 yr). Follow-up ranged from 1 to 19 years (mean, 5 yr). Patients were seen quarterly for the first year, biannually during the second year, and annually thereafter if there was no evidence of metastatic disease. Thirty-five percent (68 patients) had clinical stage C disease, and 90% (175 patients) had pathologic stage C disease. Most patients had only one lymph node involved, two-thirds had a large tumor bulk ($>10 \text{ cm}^3$), and one-half of the total had undifferentiated cancer. Unfavorable variables, such as residual cancer (31%) and elevated acid phosphatase level (17%), were also noted (table 2). Of those patients who underwent surgery, 5 or more years had elapsed for 93 of them, 10 or more for 28, and 15 years or more for 9.

Of the various adjuvant treatment modalities (orchiectomy, diethylstilbestrol, irradiation), orchiectomy was the most beneficial. Although orchiectomy was eventually performed in almost all patients who had progression, overall immediate orchiectomy was performed in only 109 patients (56%). Overall, the probability of nonprogression at 5, 10, and 15 years was 56%, 47%, and 47%, respectively. Projected

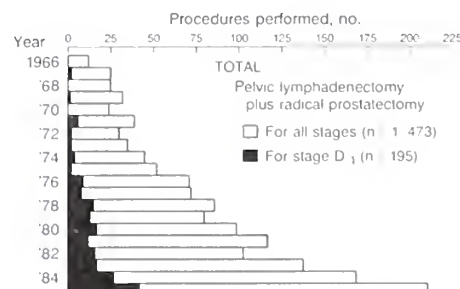


FIGURE 6.—Number of radical retropubic prostatectomy procedures performed at the Mayo Clinic from 1966 to 1985.

TABLE 2.—Data on 195 patients with pathologic stage D1 (pT0–3 N1,2 M0) prostate cancer

Pathology	Patients	
	No.	Percent
Grade		
2	99	51
3, 4	96	49
Tumor bulk (prostate only)		
>10 cm ³	74	38
≤10 cm ³	121	62
No. of positive nodes ^a		
1	85	44
2	48	25
3	23	12
4	16	8
≥5	20	11
Residual cancer		
Yes	61	31
No	134	69
Elevated acid phosphatase		
Yes	33	17
No	162	83

^a Data are for 192 patients only.

absence of local progression at 10 years was 80%, with 12 patients still under observation at this time (fig. 7). Projected survival (fig. 8) at 5 and 10 years was 83% and 68%, respectively, which is similar to the expected survival of an age-matched control group of the North Central United States. Analysis according to cause-specific death projected a 5- and 10-year survival of 92% and 83%, respectively (fig. 9).

Fourteen patients (7.2%) died of cancer. Their age (mean, 61 yr) and number of positive nodes (mean, 2.14 ± 2.0) were not significantly different from the age and positive nodes of those who did not die of the disease. Only 3 patients had received early adjuvant orchiectomy, 5 had received diethylstilbestrol, 3 had irradiation and orchiectomy in 2 of these 3, and 3 had no early adjuvant treatment.

The period of progression-free survival ranged from 9 to 115 months (mean, 53 mo), and the survival ranged from 36

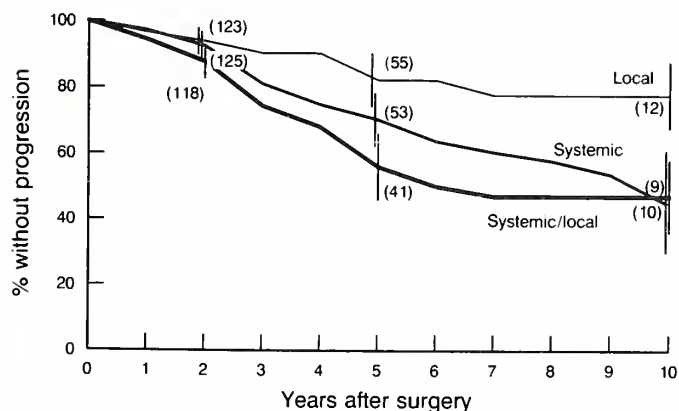


FIGURE 7.—Kaplan-Meier curves of nonprogression for 195 patients with stage D1 prostate cancer who had undergone radical prostatectomy according to systemic, local, and overall progression.

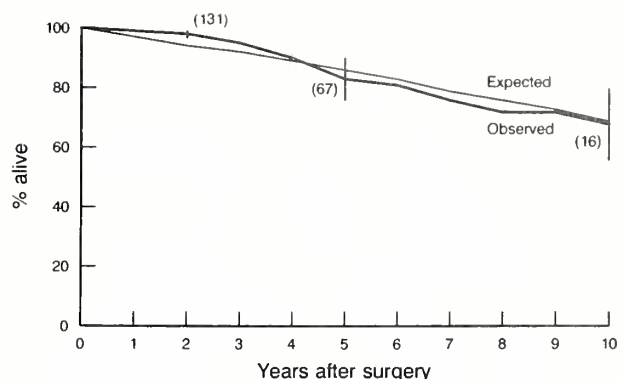


FIGURE 8.—Kaplan-Meier survival curve of 195 patients with stage D1 prostate cancer who had undergone radical prostatectomy with or without adjuvant treatment, compared with the expected survival.

to 212 months (mean, 80 mo). As seen previously in the treatment of stage pT3 disease, adjuvant treatment significantly reduced local recurrence, which was noted in 22 (11%) of the 195 patients. Of these, 17 had no adjuvant treatment originally, 3 had orchiectomy, and 2 had received diethylstilbestrol. Again, residual cancer did not correlate with progression, in particular local recurrence (fig. 10), because most patients with residual cancer received adjuvant treatment. Of the patients with residual cancer, adjuvant orchiectomy or radiation resulted in a 90% and 100% local recurrence-free survival, respectively. Conversely, overall, 20% of the patients had local recurrence at 5 years; this group included patients who had received diethylstilbestrol or who had no adjuvant treatment because they originally were without residual disease. This percentage was significantly higher ($P < .03$) than for patients receiving adjuvant orchiectomy.

A presurgical elevated acid phosphatase level (33 patients), which is assumed to be associated with an extremely poor prognosis, was not related to progression or survival. At 5 and 10 years, survival rates for patients with an elevated acid phosphatase level or elevated tartrate-inhibited fraction of the acid phosphatase, or both, were not significantly different from survival rates for patients who had no elevated acid phosphatase level, with or without adjuvant orchiectomy. This applied also to the results of nonprogression. Once patients experienced progression, the probability of survival

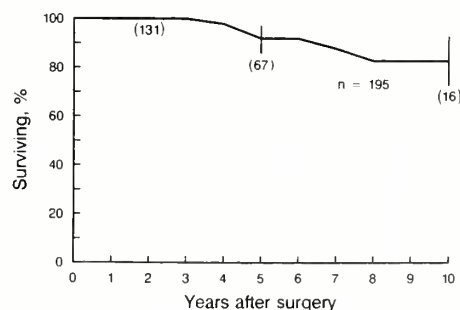


FIGURE 9.—Kaplan-Meier survival curve of 195 patients with pathologic stage D1 prostate cancer, according to cause-specific death (prostate cancer).

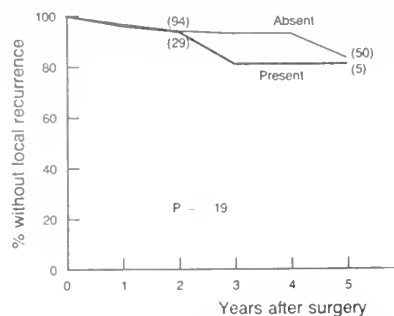


FIGURE 10.—Kaplan-Meier curves of survival until local recurrence in 195 patients with stage D1 prostate cancer who had undergone radical prostatectomy, according to presence (61 patients) or absence of residual cancer.

was low. Of the 57 patients who had progression, usually without initial adjuvant treatment, 20 died after a median follow-up time of only 2.5 years. Five-year survival of patients who did not have immediate orchiectomy (although they usually underwent orchiectomy later) was 64% and was only 33% for patients who underwent immediate orchiectomy (fig. 11). The numbers in these 2 groups are too small for any definite conclusion to be made, but for patients who failed after early adjuvant orchiectomy (14 of 109 or 13%), the probability for longer survival tended to be poorer than for those who had not received immediate adjuvant orchiectomy (43 of 86 or 50% failed).

Of the pathologic variables examined, i.e., tumor grade, seminal vesicle involvement, tumor bulk, and number of nodes, only the number of nodes was associated with progression but not survival (fig. 12). Patients with one positive node who did not receive adjuvant treatment had a significantly better disease-free survival ($P < .02$) than did those with two or more nodes involved.

Because follow-up of many patients had been less than 5 years, projected overall survival rates (in particular, survival rates according to cause-specific deaths) may not show significant differences because of the lag period. Therefore, data on the 93 patients who had follow-up of 5 years or more were analyzed. Immediate orchiectomy resulted in a 5- and 10-year nonprogression rate of 84% and 78%, respectively, compared with 46% and 35% ($P = .0009$) when no immediate orchiectomy was performed (fig. 13). Survival at 5 and

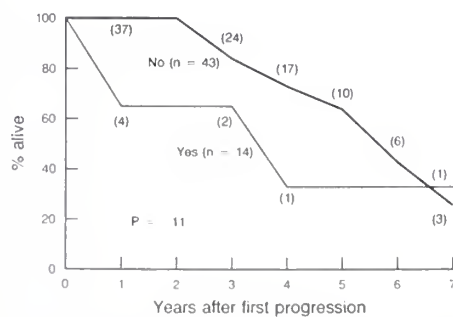


FIGURE 11.—Kaplan-Meier curves of survival after first progression in 57 patients with stage D1 prostate cancer who had undergone radical prostatectomy, according to whether they had immediate adjuvant orchiectomy.

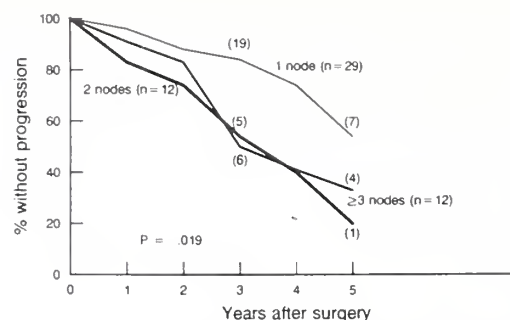


FIGURE 12.—Kaplan-Meier curves of nonprogression for 53 patients with stage D1 prostate cancer who had undergone radical prostatectomy without immediate adjuvant treatment, according to number of positive nodes.

10 years for the orchiectomy group was 87% and 76.5%, respectively, and for the nonimmediate orchiectomy group, 77.5% and 48.5%, respectively. Survival in regard to cause-specific death only (fig. 14) at 5 and 10 years in the immediate orchiectomy group was 92% and 80%, respectively, and was 91.5% and 84.5%, respectively, for the nonimmediate orchiectomy group (no significant difference).

These results may reflect not only various treatment modalities but also various disease characteristics. Therefore, in the absence of reliable tumor/host variables (e.g., grade, bulk, and number of nodes) and in the search of a tumor variable that might be a reliable predictor, flow cytometric analysis was performed on the prostate cancer specimens of our patients in regard to DNA ploidy pattern (21). Preliminary results indicated that ploidy pattern is related to disease outcome, particularly in regard to adjuvant hormonal (i.e., orchiectomy) treatment. If these initial data can be confirmed by an extensive analysis of more patients and longer follow-up, the use of DNA pattern determination may be highly significant as a prognostic indicator. This analysis is particularly important because all pathologic variables in stage D1 disease have not proved useful in the prediction of disease outcome.

In conclusion, prostatectomy as a means for effective local control provides tumor debulking; immediate orchiectomy (as opposed to diethylstilbestrol, which can be associated with a compliance problem) is a most effective form of

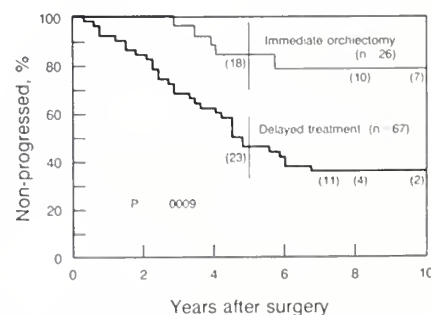


FIGURE 13.—Kaplan-Meier curves of nonprogression for 93 patients with stage D1 prostate cancer (follow-up ≥ 5 yr) who had undergone radical prostatectomy, according to immediate adjuvant orchiectomy or delayed treatment.

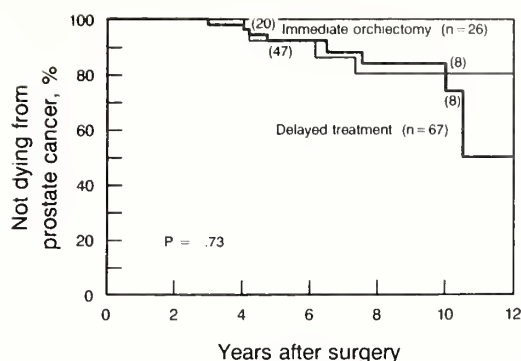


FIGURE 14.—Kaplan-Meier survival curves of cause-specific death (prostate cancer) of 93 patients with stage D1 prostate cancer (follow-up ≥ 5 yr) who had undergone radical prostatectomy, according to immediate adjuvant orchiectomy or delayed adjuvant treatment.

androgen ablation, which may achieve some systemic control of androgen-responsive cells. The favorable results in the treatment of stage D1 disease with adjuvant orchiectomy suggest that tumors of many patients retain, to some degree, androgen-dependent homogeneity, despite pelvic nodal involvement and thus systemic disease. Accumulated evidence from experience at the Mayo Clinic and that at other institutions indicates that orchiectomy or prostatectomy alone is ineffective for this stage of the disease.

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Long-term Results of Radical Prostatectomy in Clinically Localized Prostate Cancer: Experience at The Johns Hopkins Hospital

Herbert Lepor,* Patrick C. Walsh^{1,2}

ABSTRACT—The objectives of our retrospective long-term analysis of radical prostatectomy at The Johns Hopkins Hospital are to determine the efficacy of radical prostatectomy and the optimal statistical method for ascertaining survival following therapeutic intervention for men with clinically localized prostate cancer. The duration of survival and the cause of death were ascertained for 57 men with clinical stage B1 prostate cancer who had radical prostatectomies at The Johns Hopkins Hospital between 1951 and 1963. The absence of metastatic disease was determined by radiographic survey of the bones only. The survival curve determined by the direct method was virtually identical to the projected survival curve for a 62-year-old man in 1960. The cause-specific actuarial survival analysis indicated that only 14% of the men with stage B1 disease and a 15-year life expectancy will develop metastatic prostate cancer following radical prostatectomy. The cause-specific survival curve plateaued after 10 years, which indicated that the majority of men surviving 10 years free of disease are cured of the disease. Survival analysis was also determined by the direct method for 48 men with clinical stage B2 prostate cancer who had undergone radical prostatectomy between 1951 and 1963. Overall, the survival rates for these men were considerably lower than those for similarly treated men with clinical stage B1 disease. The survival curves following radical prostatectomy for men with stage B1 disease and clinical stage B2 disease pathologically confined to the prostate were similar. Radical prostatectomy for stage B1 disease was performed with minimal morbidity, and potency was preserved in most patients with the use of nerve-sparing modifications. A review of the clinical experience at The Johns Hopkins Hospital indicates that excellent local disease control was achieved following radical prostatectomy. On the basis of curability, morbidity, and control of local disease, radical prostatectomy represents a very effective treatment for clinically localized prostate cancer. Cause-specific survival analysis represents a useful statistical method for the ascertainment of survival rates for men with this disease.—NCI Monogr 7:117-122, 1988.

The optimal treatment of clinically localized prostate cancer represents one of the most controversial issues in the management of genitourinary cancers. The therapeutic options that have been advocated for the management of this disease include radical prostatectomy, external-beam radiotherapy, interstitial radiotherapy, hormonal therapy, transurethral resection of the prostate, and no treatment (1-6). A recent survey of the patterns of care for prostate cancer

sponsored by the American College of Surgeons revealed that there is no consensus for the treatment of clinically localized disease (7).

Many factors contribute to the controversy regarding the optimal management of clinically localized prostate cancer. The natural history of the disease remains poorly defined. The metastatic potential of stage A1 disease was not recognized until recently (8,9). Because the majority of studies reported in the literature are nonrandomized and the clinical series reported lack standardization of staging criteria and methods of statistical analysis, it is difficult for one to compare the efficacy of various therapeutic options and to determine the efficacy of specific therapeutic modalities due to the indiscriminate use of adjuvant hormonal therapy. The resolution of the controversy regarding the optimal treatment requires a randomized study with long-term clinical follow-up. Alternatively, the relative efficacy of therapeutic options can be inferred from nonrandomized, nonconcurrent clinical series that have been reported with long-term follow-up.

Our objectives in this retrospective long-term analysis of radical prostatectomy at The Johns Hopkins Hospital are to determine curability, morbidity, and control of local disease following radical prostatectomy for clinically localized prostate cancer. The lack of standardized methods for reporting survival analysis compounds the potential misinterpretation of nonrandomized, nonconcurrent studies of men with this disease. Therefore, we analyzed the survival data using various statistical methods to determine appropriate methods for ascertaining survival (curability) following therapeutic intervention.

HISTORICAL PERSPECTIVE

Although radical perineal prostatectomy was originally described by Kuchler in 1866 (10), Young in 1905 (11) modified the operative procedure and made it more anatomic and practical. Since that time, there have been a few minor but important modifications of Young's technique (12-14).

The criteria for patient selection were clarified in 1968 when Jewett (15) reported The Johns Hopkins Hospital experience with radical prostatectomy for the palpable nodule of prostate cancer. Between 1909 and 1951, 103 men with a palpable nodule of prostate cancer underwent radical prostatectomy, and all had follow-up for at least 15 years or until the time of death; 27% of the men with a palpable nodule of histologically differentiated and limited prostate cancer survived 15 years free of recurrence. Walsh and Jewett (16) reported a more recent series of radical prostatectomies performed for men with stage B1 disease between 1951 and 1963. The survival of patients with clinical stage B1 prostate

¹ Department of Urology, The Johns Hopkins Medical Institutions, Baltimore, MD.

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* Reprint requests to: Herbert Lepor, M.D., Division of Urology, Department of Surgery, The Jewish Hospital of St. Louis at Washington University Medical Center, 216 South Kingshighway, St. Louis, MO 63110.

cancer who had undergone radical prostatectomy paralleled the survival curve of a 62-year-old man in the year 1960. Elder et al. (17) recently reviewed the long-term survival of men with clinical stage B2 prostate cancer who had undergone radical perineal prostatectomy at The Johns Hopkins Hospital between 1951 and 1963. The survival curve for men with clinical stage B2 disease confined pathologically to the prostate paralleled that for men with clinical stage B1 disease who had this radical surgery performed. The presence of extraprostatic extension was associated with a marked decrease in survival.

Despite the curative potential of radical prostatectomy, many patients and their physicians selected alternative forms of treatment, inasmuch as most patients were impotent after the operation. On the basis of anatomic studies performed in the male fetus and stillborn infants, Walsh modified the technique for radical retropubic prostatectomy to preserve sexual function (14,18). Sexual function can now be preserved in 70% of the men with clinically localized prostate cancer who undergo radical prostatectomy (19).

STAGE B1 DISEASE

Survival Analysis

The duration of survival and the cause of death were determined for 57 men with clinical stage B1 prostate cancer who underwent radical prostatectomy at The Johns Hopkins Hospital between 1951 and 1963. The absence of metastatic disease was determined by a radiographic survey of the bones. The majority of cases were staged with serum acid phosphatase determinations. Staging pelvic lymphadenectomies and bone scans were not performed. Of the 57 patients, 54 had pathologic evidence of stage B disease. This is a unique series because all patients were carefully staged clinically and pathologically, and none received adjuvant hormonal therapy.

Survival analysis was calculated according to the direct, the all-cause actuarial (Kaplan-Meier), and the cause-specific actuarial methods (20). The percentage of patients alive at the end of a specific interval is calculated with the direct method. In the all-cause and cause-specific methods, the record of each patient for the duration of follow-up is used, and therefore they include patients still alive at the end of the study and those lost to follow-up. The procedure is nonparametric because it does not assume a particular functional form, such as a negative exponential function, for the survival curve. A distinction is made between deaths from prostate cancer and deaths from causes unrelated to cancer. The primary advantage of cause-specific analysis is that this method controls for the effect on survival of various covariables, such as general medical condition and age. Therefore, cause-specific survival analysis precisely indicates the impact of a therapeutic modality on survival because only death from a specific disease entity is evaluated.

The 5-, 10-, and 15-year all-cause survival rates were determined with the direct method (fig. 1). The 5-, 10-, and 15-year all-cause survival rates were 83%, 63%, and 51%, respectively. The all-cause survival curve was compared with a projected average survival curve for a 62-year-old man in the year 1960 (fig. 1). The observed survival curve for men with clinical stage B1 prostate cancer following radical peri-

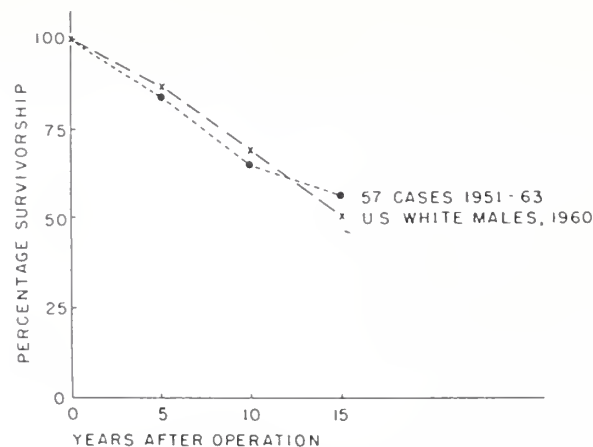


FIGURE 1.—All-cause survival curves for 57 men with stage B1 prostate cancer who had radical prostatectomies at The Johns Hopkins Hospital between 1951 and 1963. Curves were determined by the direct method.

neal prostatectomy was virtually identical to the projected survival curve of age-matched men selected from the general population.

The survival rates were calculated with the use of the Kaplan-Meier procedure (fig. 2). Deaths directly attributed to prostate cancer and deaths unrelated to cancer are not differentiated when the all-cause actuarial survival analysis is used. The 5-, 10-, and 15-year all-cause actuarial survival rates are virtually identical to the values calculated with the direct method. The all-cause survival curve decreases at a constant rate throughout the entire follow-up interval. This is not unexpected due to the advanced age of the men with prostate cancer who were followed up over a long interval.

The survival rates were also calculated by cause-specific actuarial survival methods (fig. 2). A comparison of the all-cause and cause-specific survival curves indicates that the primary cause of mortality in surgically treated men with stage B1 disease is not cancer related. The cause-specific actuarial survival curve indicates that only 14% of the men with stage B1 disease and 15-year life expectancy will die with metastatic prostate cancer following radical prostatectomy. The cause-specific survival curve plateaus after a follow-up of 10 years, which indicates that the majority of men surviving 10 years are cured of their disease. Using disease-specific survival analysis, Bagshaw (21) has recently analyzed the survival of men with clinically localized prostate cancer (stages A and B) undergoing radiotherapy. The disease-specific survival curve following radiotherapy continues to decline at a constant rate. Freiha and Bagshaw (22) recently observed that the incidence of positive biopsies following external-beam radiotherapy for stage B disease was 50%. A positive biopsy after irradiation is associated with a significantly greater tendency for disease progression (23). It is possible that the continuous decline of the disease-specific survival curve following radiotherapy is attributed to the failure of radiotherapy to eradicate completely the local disease in these patients.

The major limitation of all-cause survival analysis is that this procedure does not allow for the inclusion of potentially significant covariables such as age, race, and general medical

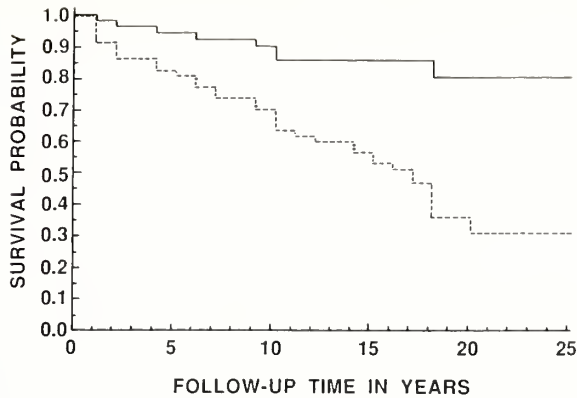


FIGURE 2.—Actuarial survival rates for 57 men with stage B1 prostate cancer who had radical prostatectomies at The Johns Hopkins Hospital between 1951 and 1963. Curves were determined by all-cause (—) and cause-specific (----) actuarial survival analysis.

condition. The all-cause survival rate for a group of young healthy men with localized prostate cancer undergoing any therapeutic intervention will exceed that of an elderly debilitated group of men receiving comparable treatment. This phenomenon is illustrated by determination of the nonprostate cancer, prostate cancer, and all-cause mortality rates as a function of age at the time of radical prostatectomy (table 1). The likelihood of mortality from nonprostate cancer-related causes increases stepwise as a function of increasing age. The mortality rate of prostate cancer (cause-specific) is independent of age. The all-cause mortality rate according to age and that of cancer other than prostate are parallel. We used the Cox proportional hazards method (24) as modified by Breslow (25) to evaluate the effect of age on survival and to compute the relative risk for age (table 2). This analysis clearly indicates that the all-cause mortality rates are age dependent ($P = .003$), whereas the cause-specific (prostate cancer) mortality rates are independent of age ($P = .85$).

When comparing nonrandomized, nonconcurrent studies, one must consider that parameters other than therapeutic measures may account for survival differences. Specifically, if there is a substantial discrepancy in the interval before patients are initiated into studies, factors such as general advances in medical treatment may account for some of the observed survival differences (26). When nonconcurrent comparative studies of men with clinically localized prostate cancer are analyzed, improvements in the criteria for select-

TABLE 1.—Mortality rate by age and by death category

Age, yr	No. of patients	Mortality, %		
		Nonprostate cancer	Prostate cancer	All causes
50-54	9	11.1	11.1	22.2
55-59	18	38.9	22.2	61.1
60-64	15	60.0	6.7	66.7
65-69	12	58.3	16.7	75.0
70-74	3	100.0	0.0	100.0
Total	57	47.4	14.0	61.4

TABLE 2.—Risk of death for patients over 50 yr of age relative to 50-yr-old patients^a

Age, yr	Relative risk	
	All causes	Prostate cancer
50	1.0	1.0
55	1.37 (1.02, 1.85)	0.94 (0.48, 1.82)
60	1.89 (1.04, 3.41)	0.88 (0.24, 3.30)
65	2.59 (1.06, 6.29)	0.83 (0.11, 5.98)
70	3.55 (1.09, 11.62)	0.78 (0.06, 10.86)

^a Risk was estimated from Cox model. Values in parentheses are 95% confidence intervals.

ing candidates for treatment may also account for observed survival differences. The limitations of nonconcurrent studies are illustrated by a review of The Johns Hopkins Hospital experience with radical prostatectomy for stage B1 disease (table 3). During the 1909-1951 interval, 103 men with stage B1 disease underwent radical prostatectomy, and the 15-year disease-free survival was 27%. Fifty-seven men with stage B1 disease underwent radical prostatectomy between 1951 and 1963, and the 15-year disease-free survival was 51%. The staging criteria were similar in these series except that the majority of men in the more current study had serum acid phosphatase determinations. The significant survival difference observed in these series may be explained by advances in medical care and surgical technique. When modern radiotherapy series are compared with The Johns Hopkins Hospital experience with radical prostatectomy, significant advances in staging criteria and overall improvements in medical care are likely to favor the survival data following radiotherapy. Therefore, when modern radiotherapy series are compared with historical radical prostatectomy series, the impact of the time interval and the improvement in patient selection must not be overlooked.

Morbidity

Jewett (15) reviewed the morbidity following radical prostatectomy for a series of radical perineal prostatectomies performed at The Johns Hopkins Hospital for stage B1 disease between the years 1909 and 1951. The operative mortality in this series was only 1%. Anastomotic strictures and thrombophlebitis occurred in 7% and 2% of the patients, respectively. Although intraoperative injury to the rectum occurred in 4% of the patients, none developed a rectal fistula. Mild stress incontinence occurred in 3% of the patients, and no man was totally incontinent. Following radical perineal prostatectomy, 90% of the men were impotent. Overall, even in the preantibiotic era, radical prostatectomy was performed

TABLE 3.—Disease-free survival at 15 yr following radical prostatectomy for stage B1 disease

Date of prostatectomy	No. of patients	Survival, %
1909-1951	103	27
1951-1963	57	51

with minimal intraoperative and perioperative complications or long-term sequelae other than impotence.

Impotence following radical prostatectomy occurs from injury to the autonomic innervation of the corpora cavernosa. On the basis of anatomic dissections performed in the male fetus and stillborn infants, Walsh and Donker (18) delineated the anatomic pathway of the cavernous nerves, and the technique for radical retropubic prostatectomy was modified so that the autonomic innervation to the corpora cavernosa was preserved (14). Walsh and Lepor (1) recently reported the morbidity in 290 men on whom radical prostatectomies were performed at The Johns Hopkins Hospital between 1982 and 1985 using the nerve-sparing modifications. There were no intraoperative deaths or rectal injuries. Pulmonary emboli and ureteral injury occurred in less than 1% of the patients. No patient who has been followed up for at least 1 year was totally incontinent. No patients wear urinary appliances or have required anti-incontinence surgery; less than 5% of the patients wear a small pad in their trousers that may be changed once or twice a day. Seventy percent of the patients are potent. The complication rate following radical prostatectomy with modern surgical techniques remains low. The decision for alternative therapy based on relative morbidity does not seem to be justified.

Local Disease Control

Unfortunately, not all men with clinically localized prostate cancer are cured following radical prostatectomy because of the presence of micrometastatic disease. However, complete excision of the local tumor burden in these patients may provide excellent local disease control. Therefore, when the relative efficacy of radical prostatectomy for men with clinically localized prostate cancer is considered, these parameters are relevant because local disease control and prolongation of disease-free survival may enhance the quality of life. The long-term experience at The Johns Hopkins Hospital provides some insight into the local disease control following radical prostatectomy.

Local recurrence following therapeutic intervention may represent histologic, palpable, or symptomatic local recurrence. The clinical significance of local recurrence is the development of symptoms of bladder outlet obstruction and the potential for malignant cells to metastasize. Because the prostatic fossa is empty after radical prostatectomy, any local recurrence of significant volume is readily discernible by rectal examination. On the other hand, after radiotherapy, the prostatic fossa is indurated, and the distinction between changes due to radiation effects and those due to recurrence is not readily apparent. Because most consider the digital rectal examination inadequate for assessing local disease control following radiation therapy, surgeons at some centers are routinely performing postirradiation needle biopsies. Although a consequence of local recurrence is the development of symptomatic bladder outlet obstruction, few long-term studies following radiotherapy or radical prostatectomy address the issue of symptomatic local recurrence.

Local (palpable) disease recurrence developed in 14 of 86 men (16%) with pathologic stage B disease who underwent radical prostatectomy between 1909 and 1951 (13). Because of improvements in clinical staging that have developed since

1951, the vast majority of men with clinical stage B1 disease have tumors pathologically confined to the prostate. Overall, we can expect long-term local disease control in at least 85% of the men with stage B1 disease who receive this surgical treatment.

STAGE B2 DISEASE

Radical prostatectomy has been offered for the treatment of stage B2 prostate cancer with the realization that some men with clinically undetectable micrometastatic disease will not be cured. Elder et al. (17) recently reviewed the long-term experience with radical prostatectomy for stage B2 disease at The Johns Hopkins Hospital. The duration of survival and the cause of death were determined for 48 men with clinical stage B2 prostate cancer who underwent radical prostatectomy at The Johns Hopkins Hospital between 1951 and 1963 (fig. 3). The absence of metastatic disease was ascertained by plain-film radiograms of the bones only. Survival was determined by the direct method. We are currently evaluating this clinical series using cause-specific survival analysis. The 5-, 10-, and 15-year disease-free survival rates following radical prostatectomy were 75%, 50%, and 25%, respectively. The observed survival curve calculated by the direct method for men with clinical stage B2 disease is far less favorable than that for men with clinical stage B1 disease. The survival data were stratified according to the presence or absence of pathologic evidence of extraprostatic extension (fig. 4). When the tumor was pathologically confined to the prostate, the 5-, 10-, and 15-year disease-free survival rates were 63%, 63%, and 50%, respectively; when the tumor extended beyond the prostate (seminal vesicle invasion), the rates were 75%, 40%, and 13%, respectively. Thus the cure of men with clinical stage B2 disease is influenced by pathologic stage. The observed 15-year disease-free survival rate calculated by the direct method for clinical stage B2 disease pathologically confined to the prostate was equivalent to the observed survival rate for men with clinical stage B1 disease.

Men with clinical stage B2 disease pathologically confined to the prostate are excellent candidates for radical prostatec-

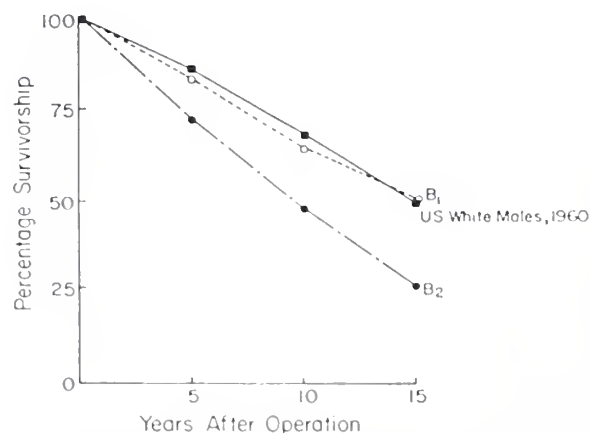


FIGURE 3.—All-cause disease-free survival curves for 48 men with clinical stage B2 prostate cancer who had radical prostatectomies at The Johns Hopkins Hospital between 1951 and 1963. Curves were determined by the direct method.

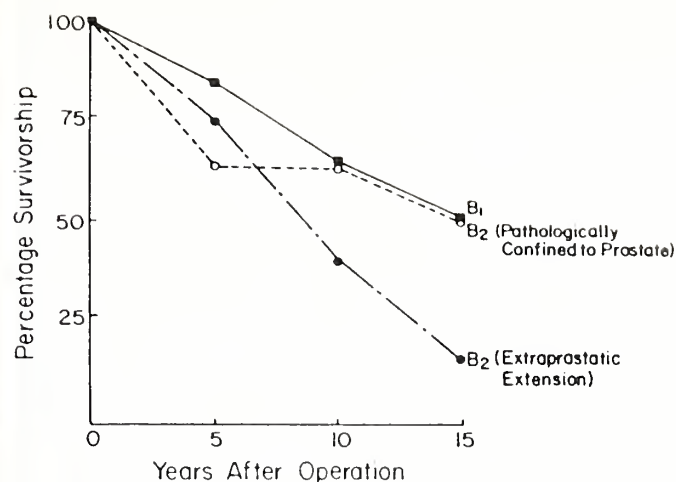


FIGURE 4.—Influence of pathologic stage on disease-free survival in men with clinical stage B2 prostate cancer who had radical prostatectomies at The Johns Hopkins Hospital between 1951 and 1963. Survival data are analyzed for men with stage B1 disease (—); stage B2 disease pathologically confined to prostate (---); and stage B2 disease pathologically extending beyond prostate (— · —).

tomy. Recent advances in clinical staging criteria have improved physicians' ability to recognize those with clinical stage B2 disease who have no pathologic evidence of extraprostatic extension. When clinical staging criteria were limited to plain-film radiograms and serum acid phosphatase determinations, only 31% of the men with clinical stage B2 disease were found to have pathologically confined tumors. Between 1982 and 1984, 22 men with clinical stage B2 prostate cancer underwent radical prostatectomy. The staging criteria in this group of patients included staging lymphadenectomies, serum acid phosphatase determinations, and radionuclide bone scans. Only 25% of the prostatectomy specimens had pathologic evidence of seminal vesicle extension (19). Despite improvements in staging criteria, radical prostatectomy is not an optimal treatment for all men with clinical stage B2 disease. The clinical dilemma is whether to withhold a potentially curative treatment for 73% of the patients or offer a potentially noncurative treatment for 27% of those with presumed micrometastasis. Hopefully, future improvements in imaging modalities, such as transrectal ultrasound or magnetic resonance imaging, in conjunction with new approaches to pathologic evaluation of biopsy specimens will aid in the identification of the ideal candidate for surgical cure.

CONCLUSIONS

The long-term experience with radical prostatectomy at The Johns Hopkins Hospital was reviewed for evaluation of the efficacy of this therapeutic option for the treatment of localized prostate cancer. The criteria for evaluation following radical prostatectomy included curability, morbidity, and local disease control.

Direct method calculations showed that the survival curves for men with clinical stage B1 disease and for men with clinical stage B2 disease pathologically confined to the pros-

tate were identical to the projected survival curve for a 62-year-old man in 1960. Radical prostatectomy usually results in cure when the tumor is pathologically confined to the prostate. Although men with stage B1 disease are the optimal candidates for this radical surgery, it is likely that most men with clinical stage B2 disease, according to modern staging criteria, may also be cured of their disease following radical prostatectomy.

The survival rate of men with clinical stage B1 disease who had undergone radical prostatectomy was ascertained by cause-specific survival analysis; the primary advantage of this analysis is that the impact of a specific therapeutic modality on survival is more precisely determined when death from a specific disease entity is evaluated. The cause-specific survival curve for men with clinical stage B1 disease plateaued at 10 years, which indicated that the majority of men surviving 10 years were cured of their disease. On the basis of data from this series of patients, men with clinical stage B1 prostate cancer who undergo radical prostatectomy may be told that the chance of death from prostate cancer within 15 years of surgery averages $14\% \pm 5\%$.

This long-term retrospective analysis of The Johns Hopkins Hospital experience with radical prostatectomy illustrates several fundamental caveats for comparison of non-randomized, nonconcurrent studies of radical prostatectomy and radiotherapy. Cause-specific survival analysis represents a useful statistical method for us to ascertain survival rates for men with clinically localized prostate cancer. When nonrandomized, nonconcurrent studies are compared, one must recognize that parameters other than therapeutic measures may account for survival differences. Researchers' attempts to compare modern radiotherapy series with the historical radical prostatectomy series at The Johns Hopkins Hospital are faulted due to significant advances in overall medical care and staging criteria that were available in the modern radiotherapy series.

A review of the historical data and the more recent experience with radical prostatectomy at The Johns Hopkins Hospital indicate that the operative procedure can be performed with minimal morbidity. This therapeutic option can be offered with the virtual assurance of the patient achieving urinary continence. Historically, despite the curative potential of radical prostatectomy, many patients and their physicians selected alternative forms of treatment because most patients were impotent after the surgery. Because of modern modifications in surgical technique, radical prostatectomy can be performed with preservation of potency in the majority of patients.

On the basis of curability, morbidity, and control of local disease, radical prostatectomy represents an effective treatment for clinically localized prostate cancer.

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Total Prostatectomy for Clinically Localized Prostate Cancer: Long-term Surgical Results and Current Morbidity¹

Robert P. Gibbons^{2,3}

ABSTRACT—The outcome for the first 57 successive patients who underwent total perineal prostatectomy for clinically localized prostate cancer at the Virginia Mason Clinic and who have been followed up for a minimum of 15 years is reviewed for evaluation of the long-term impact of this operation on the disease. Twenty percent of the patients had pathologic stage C disease. Recurrence developed in 11 of the 55 patients (20%) who could be evaluated, and death from prostate cancer occurred in 6 (11%) during this interval. The actual observed overall survival at 15 years or more was 60%, the actuarial survival 67%, and the cause-specific survival 89%. The current morbidity of this operation was evaluated by review of the last 50 consecutive patients who underwent this procedure and had follow-up of at least 6 months. Operative time averaged 140 minutes, and blood loss averaged 660 ml; 22% of the patients required a transfusion. Average postoperative hospitalization was 5 days. Two patients required a temporary colostomy for unrecognized rectal injury, and 2 developed a stricture requiring more than one dilation. Three patients (6%) wear pads for mild stress incontinence. One patient died of a cerebral vascular accident.—NCI Monogr 7:123-126, 1988.

The goal of those who manage localized prostate cancer should be to provide long-term disease-free survival, with minimal risk of long-term morbidity from the treatment. Of all the patients with prostate cancer, the disease is clinically localized (stage A or B) in 40%-50% of them (1). For better definition and clarification of the current role of total prostatectomy in the management of patients with clinically localized prostate cancer, the long-term surgical results and current morbidity data from the Virginia Mason Clinic are reviewed.

PATIENTS AND METHODS

We reviewed the data on 57 successive patients who underwent total perineal prostatectomy between 1954 and 1971 at the Virginia Mason Clinic and who have been followed up a minimum of 15 years to evaluate the long-term impact of this operation on this disease. No patients who underwent total prostatectomy during this interval were excluded. Two patients were lost to follow-up, leaving 55 patients who could be evaluated, 44 with clinical stage B1 and 11 with clinical stage B2 disease. Patients were judged to have a stage B1 tumor if it was only palpable in one lobe or a stage B2 tumor if it was palpable in both lobes. The average age was 59 years (range, 45-73).

Four patients who had pathologic stage C disease received adjuvant external-beam radiation therapy in the immediate postoperative period; 1 also received postoperative hormonal therapy (1 mg diethylstilbestrol daily). Otherwise, radiation therapy or hormone therapy was given only if recurrent prostate cancer was documented. None of these 57 patients had staging lymphadenectomy.

The current morbidity of total perineal prostatectomy was evaluated by a review of the records of the last 50 consecutive patients who underwent this procedure and had follow-up of at least 6 months. During this same interval, an additional 19 patients elected to undergo the modified retropubic prostatectomy in an effort to preserve sexual function. Five patients (10%) had evaluation of the pelvic lymph nodes prior to perineal prostatectomy.

Patient selection.—A patient was considered to be a candidate for total (radical) prostatectomy if he had 1) biopsy-proven tumor without palpable evidence of extension beyond the capsule or into the seminal vesicles in the opinion of 2 experienced urologists, 2) normal level of serum acid phosphatase, 3) no evidence of metastatic disease on bone x-ray or in later years on bone scan supplemented by radiographs of any abnormal areas, 4) expected survival of at least 15 years, and 5) willingness to undergo an operation. In general, a staging pelvic lymphadenectomy is only performed in patients with clinical stage A2 or B2 or high-grade (Gleason score, 8-10) lesions.

Surgical procedure and follow-up.—All patients underwent a total prostatectomy via the perineal route, which was described initially by Young (2). Following recovery from the operation, patients were followed up at 6-month intervals, with history, acid and alkaline phosphatase determinations, and rectal examinations. If the history suggested bone involvement or systemic disease, repeat bone x-rays or scans were obtained. Evidence of local failure was confirmed by biopsy. Patients were judged to be free of disease if they had 1) no history of failing health or bone pain and no evidence of local or regional disease on rectal examination; 2) normal acid phosphatase and prostate-specific antigen; and 3) normal bone scan in light of questionable bone disease.

RESULTS

Long-term

Of the 44 patients with clinical stage B1 and 11 with clinical stage B2 disease, 5 (11%) and 6 (55%), respectively, had microscopic pathologic stage C disease, for an overall incidence of 20% (table 1). Four patients with pathologic stage C disease received adjuvant external-beam radiation

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² Section of Urology and Renal Transplantation, Department of Surgery, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98111.

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TABLE 1.—Final pathologic stage of 55 patients with clinical stage B disease who were treated by total perineal prostatectomy

Clinical stage	No. of patients	Pathologic stage C	
		No. of patients	Percent
B1	44	5	11
B2	11	6	55
Total	55	11	20

therapy within 90 days of surgery. One patient died of metastatic prostate cancer 12 years later, 1 died of prostate cancer 5 years later, 1 died without evidence of prostate cancer 9 years later, and 1 is alive with no evidence of disease 17 years later.

The histologic grades of prostate cancer in all 55 evaluated patients are shown in table 2. The vast majority of patients had disease in the intermediate grades II and III.

Eleven patients (20%) developed recurrent disease; it was local in 2 patients, distant in 4, and local and distant in 5. Average time to recurrence was 7.3 years (range, 2–15). The influence of the pathologic stage on recurrence is seen in table 3. The recurrence rate was 16% during a mean of 7.6 years in patients with pathologic stage B disease and 36% during a mean of 6.8 years in patients with pathologic stage C disease.

Two patients developed a local recurrence 6 and 7 years following surgery; both patients then received external-beam radiation therapy. They are disease free 20 and 12 years, respectively, following completion of radiation therapy. Another patient received radiation therapy for local recurrence 3 years following surgery and 1 year later developed distant disease. He died of prostate cancer 3 years later.

The overall actual observed survival rate 15 years after surgery for the 55 patients with clinical stage B1 or B2 disease was 60% (table 4). During this interval, 6 patients (11%) died of recurrent prostate cancer. The mean interval to death was 10.3 years (range, 7–14). The causes of death other than recurrent cancer were cardiovascular disease in 10 patients, carcinoma of the lung in 3, and other causes (leukemia, suicide, and pneumonia) in 3. The mean interval to death from a cause other than prostate cancer was 7.3 years (range, 1–14). Overall, disease-free, and cause-specific actuarial survival curves are seen in figures 1–3.

Current Morbidity

The current morbidity observed after this operation was evaluated by review of the last 50 consecutive patients who

TABLE 2.—Histologic grades of prostate cancer in 55 patients with clinical stage B disease^a

Pathologic stage	Histologic grade				Total
	I	II	III	IV	
B	5	19	19	1	44
C	—	4	5	2	11
Total	5	23	24	3	55

^a Grading system is that of Gaeta et al. (3).

underwent this procedure and had follow-up of at least 6 months. The average operative time for a total perineal prostatectomy is 140 minutes, and estimated blood loss averages 660 ml; 22% of the patients require a transfusion. Average postoperative hospitalization is 5 days. The catheter is left indwelling for an average of 14 days following surgery. In the current series, 24 of the 50 patients (48%) had pathologic stage C disease. Eight percent of the patients had well-differentiated tumors (Gleason score, 2–4), 72% had moderately well-differentiated tumors (Gleason score, 5–7), and 20% had poorly differentiated tumors (Gleason score, 8–10).

Three patients were rehospitalized following discharge for problems relating to their surgery. The most serious postoperative complication was the rectal cutaneous fistula seen in 2 patients that required colostomies to be performed. These complications undoubtedly represented unrecognized rectal injury at the time of surgery. The colostomy was temporary in 1 patient. The second patient had a cerebrovascular accident 9 days following the colostomy that resulted in death. This was the only death in more than 350 radical perineal prostatectomies performed at this institution.

After recovery, 7 patients developed a stricture, but only 2 (4%) required more than one dilation. Forty-seven of the 50 patients (94%) have normal urinary control, and 3 (6%) wear pads for dampness. No patient has a degree of urine loss that requires the wearing of an appliance. None of the 26 patients asked has had an erection satisfactory for intercourse, but all 20 patients surveyed note that the sensation of orgasm is intact. To regain erectile function following surgery, 3 patients have had a penile prosthesis placed, and 4 use pharmaceutical means to achieve satisfactory erections.

DISCUSSION

The results of a treatment for prostate cancer can be measured by its effect on local control of the primary tumor, recurrence rate (progression-free interval), or overall, disease-free, or cause-specific survival. To understand bet-

TABLE 3.—Influence of pathologic stage B vs. stage C disease on recurrence rate, disease-free interval, and death rate^a

Pathologic stage	Patients		Recurrences		No. of yr to recurrence		Deaths from prostate cancer		No. of years to death	
	No.	Percent	No.	Percent	Mean	Range	No.	Percent	Mean	Range
B	44	80	7	16	7.6	3–15	4	9	9	7–14
C	11	20	4	36	6.8	2–12	2	18	13	12–14
Total	55	100	11	20	7.3		6	11	10.3	

^a Influence was determined 15 yr after total perineal prostatectomy in patients with clinical stage B disease.

TABLE 4.—Actual observed survival status of 55 patients with clinical stage B1 or B2 disease 15 yr after total perineal prostatectomy^a

Patients	Clinical stage		Total No.	Percent
	B1	B2		
Alive				
Disease free	27	5	32	58
With disease	0	1	1	2
Dead				
Disease free	12	2	14	25
With disease	1	1	2	4
Of disease	4	2	6	11
Total	44	11	55	100

^a Expected 15-yr survival for men aged 59 yr during these study years was 56% (4).

ter the influence of treatment for localized disease, it is necessary that one evaluate the natural history of untreated localized disease and the clinical course of patients who develop recurrences after treatment. Larson and Norlen (5) reported a 77% disease progression rate in 31 patients with clinical stage B disease who received no treatment and who had been followed for a mean of 6.5 years. Whitmore (6) reported a 54% progression rate (local and distant) in 13 untreated patients with stage B1 disease who had been followed up for 5 years. By 15 years, all the patients had disease progression. By comparison, only 20% of our surgically treated patients had progression of their disease during a similar 15-year interval.

The importance of disease control is emphasized further by the outcome for patients with newly diagnosed metastatic disease. Kramer et al. (7) have shown that 50% of the patients with positive regional lymph nodes are dead at 39.5 months, and Murphy and co-workers (8) reported that 50% of the patients with newly diagnosed bone

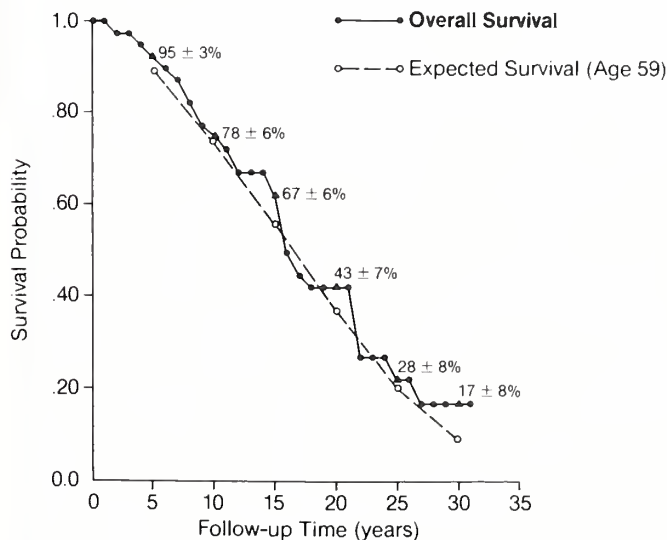


FIGURE 1.—Overall actuarial survival of 57 patients with clinical stage B prostate cancer at ≥ 15 yr after total perineal prostatectomy examined with the expected survival of 59-yr-old males in a comparable population.

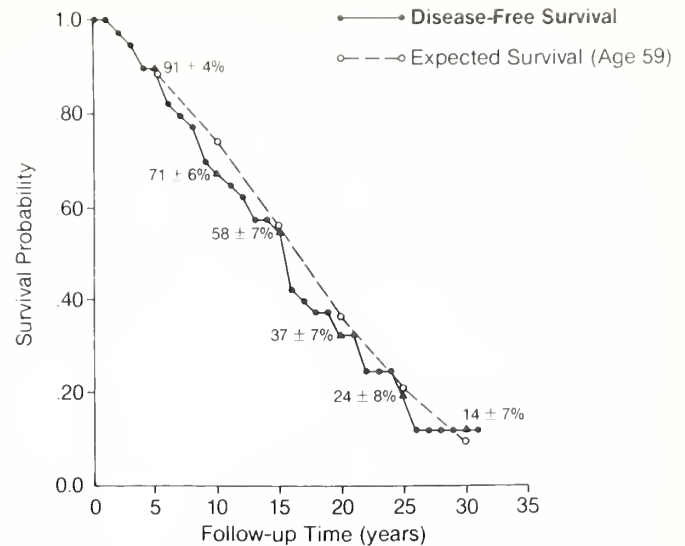


FIGURE 2.—Disease-free actuarial survival of 57 patients with clinical stage B prostate cancer at ≥ 15 yr after total perineal prostatectomy examined with the expected survival of 59-yr-old males in a comparable population.

metastases are dead at 23 months. When patients develop hormone-refractory metastatic cancer, the average survival time is 10 months (9). The morbidity of hormone-refractory metastatic prostate cancer is significant. Common sequelae in the months prior to death are bone pain and anemia from bone marrow invasion; bladder dysfunction (retention, incontinence, and hematuria); urinary tract infection; anorexia; and uremia from obstructed ureters. The 80% recurrence-free control rate observed 15 years or more after total prostatectomy simply has not been recorded with the other available treatment modalities for prostate cancer and represents a significantly improved quality of life over that of the patient who develops a recurrence.

Further evidence that treatment can influence the natural history of the disease can be seen by a comparison of the

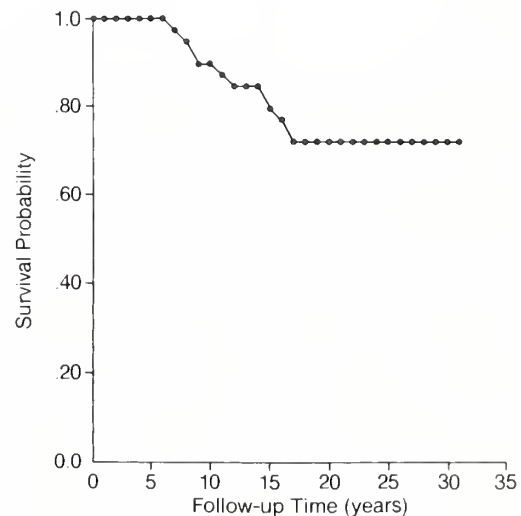


FIGURE 3.—Cause-specific actuarial survival of 57 patients with clinical stage B prostate cancer at ≥ 15 yr after total prostatectomy.

survival of treated patients with the life expectancy of the general male population of the same age in the same region during the same interval (fig. 1). The better overall survival of these surgically treated cancer patients can be explained by effective treatment and by selection criteria that exclude poor-risk patients with significant cardiovascular, respiratory, metabolic, and other diseases. Disease-free or cause-specific survival addresses better the effectiveness of the treatment alone in preventing recurrence. Disease-free survival in this surgically treated group is comparable to expected survival for up to 30 years of observation (fig. 2). Cause-specific survival did not plateau until 17 years had elapsed because these patients with clinical stage B disease were treated with total perineal prostatectomy (fig. 3). These results emphasize the need for long-term observation in the evaluation of any new form of treatment of this disease.

Patients who undergo total prostatectomy at this time accept a very small risk for long-term permanent complications or mortality. Mild stress incontinence is infrequent. Although erectile function is usually lost following total perineal prostatectomy, Weldon and Tavel (10) recently reported a modification to the perineal approach that spared erectile potency in 56% of their patients. Walsh et al. (11) reported an 83% potency rate after modified radical retro-pubic prostatectomy. If voluntary erectile function is lost following surgery or any of the other treatment modalities used, a penile prosthesis or pharmacologic-induced erections have proved satisfactory because the sense of orgasm is intact.

An additional advantage of total prostatectomy is the benefit of pathologic study of the neoplasm. Twenty percent of the patients in the long-term series and 48% in the current series had pathologic stage C disease. When this occurs, adjuvant radiotherapy can decrease the incidence of subsequent local recurrence, and its use should be considered, particularly in patients whose tumors extend to the surgical margins or who have seminal vesicle invasion (12).

The experience at the Virginia Mason Clinic demonstrates that if disease-free, long-term survival is most important to the patient with clinically localized prostate cancer, total perineal prostatectomy remains the proven treatment of choice. Minimal risk is incurred from the oper-

ation, and the potential complications are well defined and manageable.

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Randomized Series of Treatment With Surgery Versus Radiation for Prostate Adenocarcinoma

David F. Paulson¹

ABSTRACT—In the early 1970s, a multicentered cooperative group effort was established by urologists and oncologists to examine the relative disease control provided by surgery, radiation therapy, or observation for patients with localized or regional disease. The data derived from this trial were controversial because they 1) did not support previous concepts regarding the relative impact of treatment and 2) raised provocative questions as to the interpretation of previous institutional reports that promoted a single treatment modality. The data from the randomized trial demonstrated that: 1) bipedal lymphangiography could not demonstrate accurately the presence or absence of microscopic involvement of pelvic lymphatic structures; 2) treatment selection should be based on the anatomic distribution of disease; 3) a clinician's use of first appearance of local or distant disease in a patient who was supposedly disease free after receiving the chosen therapy served as an accurate way to define the impact of the initial treatment; 4) radical surgery was more effective than radiation therapy in controlling disease that was clinically confined to the primary organ of origin; and 5) the apparent disease control produced by radiation on large-volume, localized disease might only reflect the natural history of the disease.—*NCI Monogr* 7:127-131, 1988.

Early in the 1970s, a large multi-institutional study involving investigators at 13 major medical centers and their associates at Veterans Administration Medical Centers set out to ascertain their ability to determine the accuracy of current staging studies in assessing the anatomic distribution of the host at risk and, upon identification of the anatomic distribution of disease, to compare accepted treatment modalities in the management of that disease (1,2). Patient accession began February 1975, and the last patient was entered on September 8, 1978, the day that funding was withdrawn by the National Cancer Institute. In this study, 509 men with newly diagnosed, biopsy-proven prostate adenocarcinoma were assigned a preliminary clinical stage based on rectal examination, colorimetric serum acid phosphatase levels, a plain chest x-ray, and a metastatic bone survey. The scheduling of staging studies, designed to determine the anatomic distribution of disease, was sequenced to progress from those global studies that were designed to show the most widespread evidence of disease and to focus gradually on the prostate. Thus all men with an elevated acid phosphatase were believed to have systemic disease and were excluded from the randomization schema for patients with apparently localized or regional disease. In accordance with the sequential schema, all men who demonstrated no evidence of osteoblastic disease on skeletal films were subjected to a technetium-99-mentodextra posterior

bone scan. Approximately 25% of all patients with no bony disease identified on routine skeletal x-rays had bony disease on the basis of isotopic bone scanning. The frequency of bone disease increased as the volume of local disease increased [fig. 1; (3)].

Following the exclusion of disease in the axial and appendicular skeleton, the next region assessed involved the nodal structures of the pelvis that drained the prostate lymphatics. Patients who demonstrated no evidence of bone-positive disease underwent bipedal lymphangiography, with the accuracy of the lymphogram determined by pelvic lymphadenectomy. The hypothesis was that prostate carcinoma, like most other human solid tumors, has the propensity to metastasize early to the regional lymphatics.

The lymphatics of the prostate exit the posterior aspect of the gland and involve initially the hypogastric (primary), obturator (secondary), external iliac (tertiary), and presacral (quaternary) lymphatics (4). The anatomic limits of the staging lymphadenectomy were designed not only to encompass the primary and secondary areas of nodal drainage but to leave undisturbed tertiary lymphatics lateral to the external iliac artery and vein. Thus the margins of the node dissection were limited to the triangle bordered by the external iliac vasculature, the pelvic floor, and the hypogastric vasculature; all node-bearing tissue in this area was removed, including the node-bearing tissue surrounding the obturator nerve and vessels (fig. 2). As anticipated, the incidence of node-positive disease was found to increase as the volume of local disease increased (fig. 3). When the lymphograms were interpreted by a radiologist (single review) and the results compared with the incidence of node-positive disease as determined by pelvic lymphangiography, it was noted that, when the nodes were called positive, they were positive 90% of the time. However, when they were called negative, there was a 12% false-negative call. The success of the review radiologist should be contrasted with that of the institutional lymphangiographer who had a 27% false-positive rate and a 44% false-negative rate (table 1).

In an attempt to determine whether histopathologic characteristics of the tumor tissue biopsied (to establish the diagnosis of cancer) could be used to predict the presence or absence of nodal extension, the investigators analyzed the incidence of positive nodes as a function of the Gleason sum. The product of such an analysis demonstrated that both high- and low-grade disease (determined by the Gleason sum) functioned as relatively accurate predictors of node-positive disease, equivalent to that of current imaging modalities. Eighty-seven percent of the patients with a Gleason sum less than 5 had node-negative disease, whereas 100% of those with a Gleason sum of 9

¹ Division of Urologic Surgery, Department of Surgery, Duke University Medical Center, P.O. Box 2977, Durham, NC 27710.

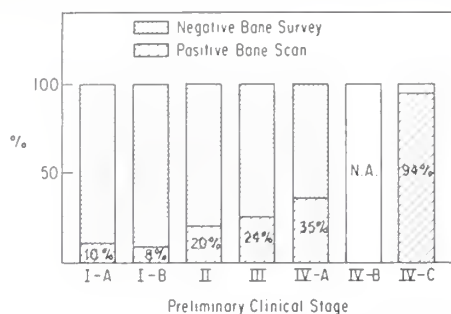


FIGURE 1.—Patients with bone disease detected by radioisotopic scanning who were considered disease free by skeletal survey. N.A. = not applicable. Reproduced with permission from (3).

or 10 had node-positive disease (table 2). With some minor variations, this general trend has been substantiated by other investigators.

Patients whose disease was confined to the prostate, determined by digital examination, and who had no evidence of bone- or node-positive disease were assumed to have organ-confined disease and were randomized to radical prostatectomy or external-beam radiation therapy. Patients with clinical stage A2 or stage B (T1-2 N0 M0) were randomized in balanced groups of 4 by institution to either radical prostatectomy or megavoltage radiation therapy (5).

Any patient with an occult focal cancer was excluded from this randomization scheme, as were any patients who had clinical stage C (T3 N0 M0) disease. Prostatectomy could be accomplished by a perineal or retropubic route; however, the anatomic limits of the dissection had to include the apex of the prostate and the seminal vesicles (fig. 4). Patients assigned to radiation therapy were treated with megavoltage equipment, i.e., the highest available energy (cobalt-60, linear accelerator, and/or betatron x-ray beam), with a minimum surface-to-axis distance of 80 cm. The field size was to have included the prostate, periprostatic region, and pelvic lymph nodes as determined

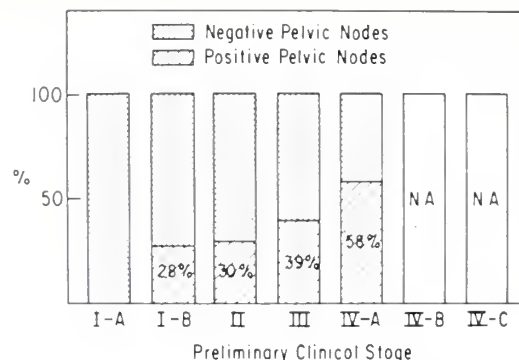


FIGURE 3.—Incidence of pelvic node extension as a function of preliminary clinical stage in patients with no bone disease as determined by isotopic bone scan. Reproduced with permission from (3).

by lymphograms and localization films. The upper margin of the radiation field was at the level of the iliac crest, the lateral margin at least 1 cm beyond the external iliac nodal chains, and the lower margin 1 cm below the inferior prostate. All fields were treated with currently accepted schemata with a total tumor dose of 4,500–5,000 rad in 40 days total elapsed time. The dose was specified from the appropriate isodose curve as a minimum dose in the volume of the prostate. An additional treatment boost of 2,000 rad was delivered to a reduced volume which had to include the prostate.

Patients were followed at 2-month intervals for the first year and at 3-month intervals thereafter. Serum biochemical profiles with acid phosphatase determinations, Karnofsky's performance ratings, and a physical examination were obtained at each follow-up; chest x-rays and isotopic bone scans were obtained at 6-month intervals. The impact of treatment was determined with first-evidence-of-treatment-failure as the end point. Investigators chose use of first-evidence-of-recurrent disease rather than survival to avoid confounding the impact of the first therapy by the subsequent application of a second

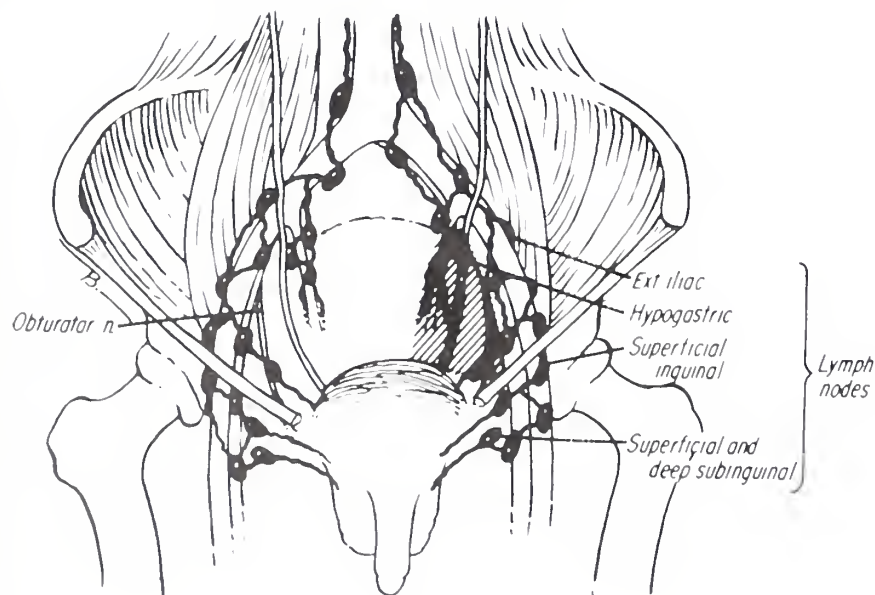


FIGURE 2.—Shaded area indicates area of limited pelvic lymph node dissection for staging of prostate carcinoma. Reproduced with permission from (3).

TABLE 1.—Lymphangiogram vs. node dissection

Lymphangiogram results	Radiologist reviewer	Node dissection	
		Positive, %	Negative, %
Positive	Referee	90	10
Positive	Institutional	73	27
Negative	Referee	21	78
Negative	Institutional	44	56

therapy that could alter the survival experience. Survival data had not been accrued because funding was withdrawn by the National Cancer Institute, and patient follow-up and data analysis could not be completed as had originally been projected. Furthermore, lack of funding precluded analysis of morbidity data and follow-up of accrued morbidity data. Treatment failure was identified by acid phosphatase elevation on two consecutive follow-ups or by the appearance of bony or parenchymal disease with or without concomitant acid phosphatase elevation. The appearance of increased isotope uptake in an area previously not demonstrating such increased uptake was identified as the presence of bony disease. The appearance of such metastatic bony disease was either progressive on subsequent scans or was accompanied by elevation of serum acid phosphatase levels. Identification of cancer in the prostate on follow-up after radiation did not signify treatment failure in assessment of relative treatment efficacy. Curves representing nonparametric estimates of time-to-first-evidence of treatment failure were generated according to the Kaplan-Meier method (6). Censored survival values representing patients without evidence-of-treatment failure at the time of last follow-up were represented by a single vertical tick on the treatment graph. Treatment efficacy in pairs of subgroups was assessed for differences by the Cox-Mantel test (7). Fifty-six patients received external-beam radiation therapy, and 41 underwent radical prostatectomy. An analysis of the time-to-failure curves of the 2 treatment groups indicates that radical surgery possessed a distinct advantage over radiation therapy in controlling disease and was significant at the .037 level (fig. 5). This study was critiqued; detractors argued that patients with more aggressive disease had been assigned to radiation therapy and the length of follow-up was too short. Analysis of the relative Gleason grade between the 2 groups indicated that the average

TABLE 2.—Node biopsy; incidence of nodal extension as a function of Gleason grade

Gleason sum	Positive, %	Negative, %	No. of patients/group
2-5	13.9	86.1	36
6	32.4	67.6	34
7	49.9	50.1	21
8	75.0	25.0	12
9-10	100.0	0	7
No diagnosis	33.0	66.1	12

Gleason grade in the radiation therapy arm was 5.1, with an average Gleason sum of 5.5 in the radical surgery arm. If the Gleason sum functions as an indicator of biologic aggressiveness, the 2 groups seem equivalent, but those undergoing surgery had a slightly higher Gleason sum than those treated by radiation. An additional 20 months of follow-up continued to demonstrate a disease control advantage of radical surgery over radiation therapy (fig. 6). In the original study design, persistent evidence of disease after biopsy and after definitive radiation therapy did not constitute failure. However, current information would suggest that this does indicate a patient population at increased risk for progression. If the biopsy-positive patients (7 of 21 who had repeat biopsies at 1 yr were positive) are included as treatment failures, the curves diverge even farther (fig. 7). The imbalance that resulted, with respect to the statistical distribution of patients, was not intentional; the study was not weighted in favor of radical prostatectomy. The study was designed for researchers to use balanced groups of 4 within each of the 13 participating institutions. Patient accession was halted on a specific day, and the randomization scheme was not allowed to go to completion. At the time the study was completed, 42 patients

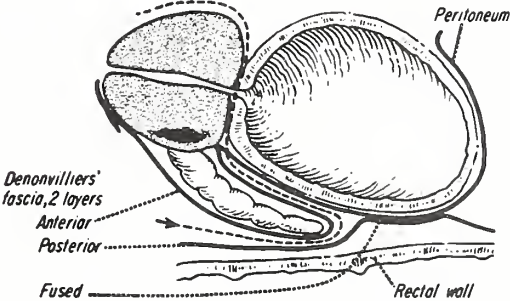


FIGURE 4.—Limits of dissection for a radical prostatectomy. Reproduced with permission from (3).

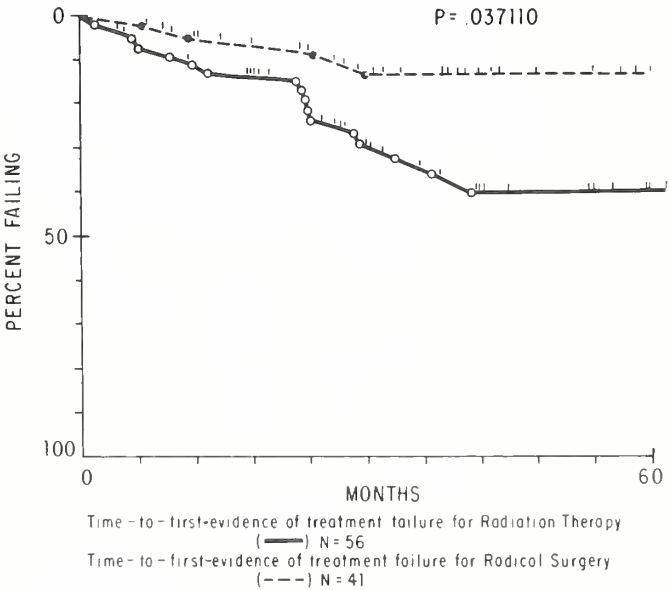


FIGURE 5.—Time-to-treatment failure for patients randomized to radiation therapy or radical surgery whose disease is confined to the prostate. Reproduced with permission from (3).

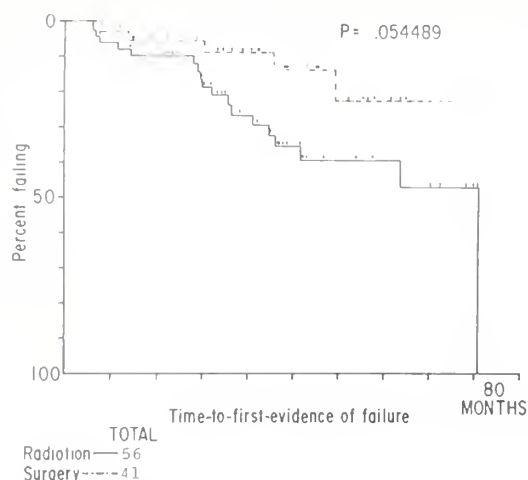


FIGURE 6.—Time-to-treatment failure for patients randomized to radical surgery or radiation therapy when the analysis is completed with an additional 20 months of follow-up. The difference between the 2 treatment arms remains distinct. Reproduced with permission from (3).

had been randomized for radical prostatectomy and 55 for radiation therapy. Four patients refused radical prostatectomy after they were randomized and demanded radiation therapy. Three patients who had been randomized to radiation therapy demanded radical prostatectomy. Thus, as the study analysis was designed to determine the impact of treatment, the final population pool under study encompassed 41 patients who received radical prostatectomy and 56 who received radiation therapy.

An additional interesting aspect of this randomized trial focused on large-volume, node-negative, localized disease (T3); the treated population was randomized to receive either radiation therapy or delayed hormonal therapy (no immediate treatment). Again, with first-evidence-of-treatment failure as the end point, the failure rates for patients actively treated by radiation therapy versus those treated by observation only are superimposed (fig. 8). One may interpret these data to demonstrate that the purported disease control impact of radiation therapy on large volume prostate cancer may reflect nothing other than the natural history of the disease.

One may ask whether these randomized trial data purporting the superior impact of radical surgery reflect insti-

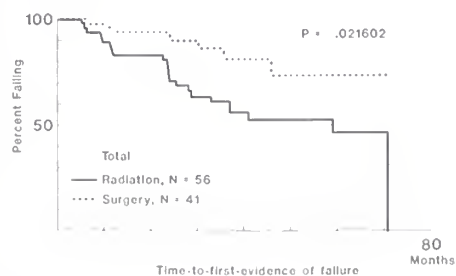


FIGURE 7.—Time-to-failure curves for patients randomized to either definitive radiation or to radical prostatectomy. Patients failing radiation in this efficacy projection include the 7 of 21 patients who had postradiation-positive biopsies.

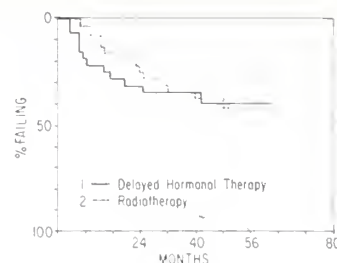


FIGURE 8.—Difference in interval to first-evidence-of-treatment failure between both groups was not statistically significant ($P = .71$). Reproduced with permission from (3).

tutional experience, wherein radical surgery is the primary form of therapy chosen for apparently localized disease. Recent review of 280 patients at Duke University Medical Center who underwent radical prostatectomy demonstrates an overall disease control response (fig. 9) similar to that seen within the randomized trial. However, the population base within this single institutional experience can be manipulated in a retrospective manner to project a most favorable outcome. When the patients were retrospectively analyzed to reflect the volume of disease in the patients being subjected to radical surgical control, patients who had small-volume, organ-confined disease demonstrated a 6% failure rate at 6 years, whereas those who had microscopic stage C cancers confined to the surgical specimen experienced a 22% failure rate at 6 years, in contrast to patients with margin-positive disease who experienced a 35% failure rate (fig. 10). These retrospective data projections document the difficulty any investigator has in providing an unbiased data analysis of nonrandomized prospective studies. Any retrospective nonrandomized series may be biased if the population is weighted by patients who have small-volume disease as identified by transurethral resection; approximately 15% to 20% of these patients will be disease free after transurethral resection alone, whereas another 15% to 20% will only have a single microscopic focus of disease in the excised surgical specimen. Inclusion of such patients in any nonrandomized series will weight the study for success. Similarly, if the population is weighted with either high- or low-grade disease (as scored by Gleason sums), that population which is weighted with

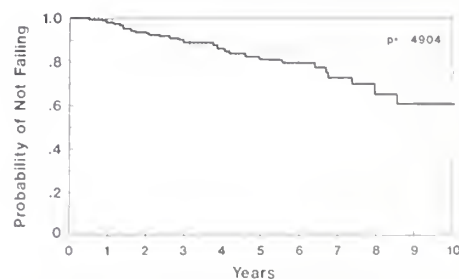


FIGURE 9.—Time-to-failure curves for patients undergoing radical prostatectomy at Duke University Medical Center (January 1, 1987; stage A vs. B) as a function of diagnosis by transrectal needle biopsy (204; heavy solid line) or transurethral resection of the prostate (76; slanted broken line).

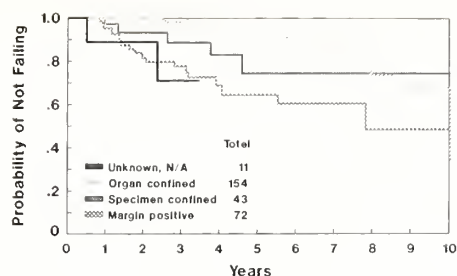


FIGURE 10.—Time-to-failure curve for the population at Duke University Medical Center (January 1, 1987) undergoing radical prostatectomy. Patient population has been segregated as to whether the tumor was organ confined, specimen confined, or margin positive.

high-grade disease will be destined to fail at a more rapid rate than that which is weighted with low-grade disease.

In conclusion, although the randomized trial as conducted at the Veterans Administration Medical Centers may be flawed, it is an unbiased, randomized, prospective trial in which physicians based treatment selection on the anatomic distribution of disease and used the most current methodology to determine the local and regional extent of malignant growth. Differences in the application of surgical and radiotherapeutic treatment at the various test sites may not

have been equivalent; however, the treatment application does reflect the real world situation and, as such, should be viewed as presenting data that are current with respect to the relative impact of the 2 treatments. For one to deny the study because it does not fit preconceived notions is improper.

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Radical Retropubic Prostatectomy With Reduced Morbidity: An Anatomic Approach

Patrick C. Walsh¹

ABSTRACT—The morbidity of radical retropubic prostatectomy for prostate cancer has been reduced through improved understanding of the surgical anatomy of the prostate. Delineation of the anatomy of the dorsal vein complex has led to modifications in the surgical technique that have reduced blood loss and improved surgical exposure. The addition of epidural anesthesia and presurgical donation of autologous blood has limited the need for the homologous transfusion of blood to 2% of the patients and has reduced the frequency of serious perioperative complications such as pulmonary emboli to 0.3%. Delineation of the anatomy of the pelvic plexus and identification of the neurovascular bundles as the macroscopic landmark of the microscopic cavernous nerves have made it possible for the surgeon to make an informed decision at the time of surgery whether the neurovascular bundles can be preserved safely or excised widely with the specimen. In all surgical approaches to prostate cancer, the primary goal must be excision of all tumor; preservation of sexual function should be of secondary concern. These considerations were addressed in the treatment of 320 consecutive patients; 74% of the men are potent postoperatively. It was necessary to excise one neurovascular bundle widely in 49 patients; 69% are potent. In addition to improvements in postoperative sexual function, the incidence of incontinence following surgery has been reduced. The total medical expenses for patients undergoing radical prostatectomy range from \$8,500 to \$9,500 and are similar to those for external-beam radiotherapy. With a reduction in overall morbidity, it is hoped that more men with localized disease will accept radical prostatectomy as the form of treatment having the greatest likelihood for cure with the expectation of an excellent quality of life postoperatively.—NCI Monogr 7:133-137, 1988.

Although radical prostatectomy is effective in the cure of localized prostate cancer, the procedure has never gained widespread popularity because the operation was perceived to be technically difficult and associated with major complications. Thus some believed that the surgery was worse than the disease itself. For this reason, patients were often advised to do nothing or were encouraged to seek treatment with potentially less effective forms of therapy because they had fewer side effects.

In offering any surgical procedure to a patient, the physician (and patient) must weigh the potential benefits versus the risks. During the past decade, we have attempted to reduce the risks of radical retropubic prostatectomy through investigations of the surgical anatomy of the prostate and adjacent structures. Over the past 10 years, the morbidity of the procedure has been reduced by lowered blood loss and improved operative exposure, reduced postoperative complications such as pulmonary emboli, and assured urinary control in virtually every patient and potency in most. At

the same time, this anatomic information has made it possible for the surgeon to obtain wider margins of resection where indicated.

REDUCED BLOOD LOSS BY IMPROVED VASCULAR CONTROL

Delineation of the anatomy of the dorsal vein complex was the single most important observation in the evolution of this surgical technique. Previously, most surgeons dreaded this operation because of the profound blood loss encountered when the dorsal vein complex at the apex of the prostate was transected. Once this had occurred, the remainder of the procedure was performed blindly and bluntly. Dissatisfied with this approach, we (1) examined the anatomy of the dorsal vein complex and Santorini's plexus and, in 1979, published an anatomic approach to the surgical management of this venous complex. The modifications in surgical technique included incisions in the endopelvic fascia near the pelvic sidewall away from the lateral venous plexus, division of the puboprostatic ligaments close to the pubis with care to avoid laceration of the superficial branch of the dorsal vein complex, and ligation of the main dorsal vein complex and its surrounding fascia anterior to the urethra. These maneuvers reduced blood loss and improved exposure so that the remainder of the procedure could be performed anatomically.

More recently, we (2) undertook further efforts to reduce blood loss during the operation. Bulldog clamps are placed temporarily on the hypogastric arteries to reduce arterial perfusion of the prostate during the early stages of the procedure. Epidural anesthesia has been shown to be effective in reducing blood loss during the operation, and all patients are encouraged to donate 3 units of their blood for autologous transfusion during the surgery. With this approach, only 2% of the patients undergoing radical retropubic prostatectomy require transfusion of a homologous unit of blood. In addition, as noted by Modig (3), there has been a marked reduction in the frequency of pulmonary emboli since the introduction of these recent advances. Of the first 125 patients, 3 developed pulmonary emboli postoperatively; one occurred 3 weeks postoperatively (when the patient was at home) and resulted in sudden death. However, following institution of routine epidural anesthesia and autotransfusions, only 1 of the next 300 patients had a pulmonary embolus. This nonfatal event occurred in a patient with a familial history of pulmonary emboli in two generations. Thus radical prostatectomy can be performed today in a relatively bloodless, controlled fashion and is rarely associated with serious postoperative complications.

¹ Department of Urology, Marburg 134, The Johns Hopkins Medical Institutions, Baltimore, MD 21205.

Shortly after the anatomy of the dorsal vein complex was delineated and this technique was applied during radical retropubic prostatectomy, several patients reported that they were fully potent postoperatively, and more stated that some sexual function was present. This new finding encouraged the suggestion in 1980 that preservation of potency following radical prostatectomy is possible (4).

SEXUAL FUNCTION AND URINARY CONTINENCE

Anatomy of Pelvic Autonomic Plexus

For years it was assumed that impotence after radical prostatectomy resulted from injury to the autonomic nerves that innervate the corpora cavernosa; however, the exact anatomic location of these nerves was uncertain. In 1982, Walsh and Donker (5) suggested that impotence was induced by injury to the pelvic nerve plexus that provides autonomic innervation to the corpora cavernosa. On the basis of this observation, the technique of radical retropubic prostatectomy was modified slightly (6-9). Although the branches of the pelvic plexus that innervate the corpora cavernosa are microscopic, they can be recognized intraoperatively because of their rather constant association with the capsular vessels of the prostate (6,10). These neurovascular bundles are located in the leaves of the lateral pelvic fascia and previously were unknowingly injured during standard radical prostatectomy. However, once the precise location of these neurovascular bundles was determined, the technique of radical retropubic prostatectomy could be modified in a way that enabled the surgeon to visualize these bundles intraoperatively and to decide whether it was safe to preserve the neurovascular bundles or necessary to excise them with a specimen. This approach has resulted in preservation of sexual function in the majority of patients and has also improved postoperative urinary continence.

Preservation of Sexual Function

The surgical technique, which is described in detail elsewhere (8,9), has now been used on 320 men who have been followed up for 1 year or longer. In all procedures, the surgeon made every attempt to excise all tumor; preservation of sexual function was of secondary concern. Of these 320 men, 259 were potent preoperatively and had sexual partners. Postoperatively, 192 (74%) are potent.

Potency, which is defined as the ability to achieve an erection that is sufficient for vaginal penetration and orgasm, returned gradually over the 1-2 years following surgery. Potency correlated with both the age of the patient and the stage of the disease (table 1). Based on clinical stage, potency returned in 93% of the patients with stage A1 disease, 72% with stage A2, 92% with stage B1N, 72% with stage B1, and 56% with stage B2. The tumor was confined within the capsule in virtually all men with stage A1 disease; therefore, it is reasonable for one to assume that both neurovascular bundles can be preserved completely in almost all men with clinical stage A1 disease and that this is responsible for the excellent return of sexual function in this group of patients. Conversely, the reduced rate of potency in men with stage B2 disease indicates that attempts at resection of more advanced tumors result in greater injury to the pelvic nerve plexus. In 49 men, we had to excise one neurovascular bundle; 69% are potent postoperatively (11). Thus one can conclude that potency can be maintained following radical prostatectomy even when it is necessary to excise one neurovascular bundle widely. The information in table 1 is very useful in our preoperative advice to patients, on the bases of age and the stage of the lesion, as to the likelihood for the return of sexual function postoperatively.

Preservation of Urinary Continence

The most disabling and feared complication following radical prostatectomy is total urinary incontinence. Fortunately, it occurs infrequently in the hands of the experienced surgeon. There are several mechanisms of urinary continence in men: the vesical neck, the passive urethral mechanism, and the external sphincter-pelvic floor mechanism. All passive mechanisms, such as the bladder neck and the intrinsic urethral mechanism, are most effective when elevated by the tonic activity of the pelvic floor. The incontinence that occurs in patients after radical prostatectomy can often be related to rigidity of the remaining posterior urethra and nonelevation of the bladder base after voluntary cessation of urination (12). Consequently, for the patient to achieve continence after radical retropubic prostatectomy, the surgeon must avoid injury to the pelvic floor mechanism, reconstruct the vesical neck so that it will provide a passive mechanism of continence, and avoid stricture formation by coapting the bladder neck to the urethra accurately. To ensure accurate coaptation of the bladder mucosa

TABLE 1.—Influence of age and clinical stage on postoperative potency in 320 men with 1-yr follow-up after radical retropubic prostatectomy

Clinical stage	Age, yr ^a											
	30-39		40-49		50-59		60-69		70-79		Total	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent	No.	Percent
A1	—	—	2/2	100	9/10	90	3/3	100	—	—	14/15	93
A2	—	—	—	—	9/10	90	4/7	57	0/1	0	13/18	72
B1N	2/2	100	4/5	80	30/31	97	11/12	92	0/1	0	47/51	92
B1	—	—	11/14	79	42/51	82	39/60	65	1/5	20	93/130	72
B2	—	—	2/3	67	15/22	68	8/20	40	—	—	25/45	56
Total	2/2	100	19/24	79	105/124	85	65/102	64	1/7	14	192/259	74

^a Values are numbers of men who had postoperative potency/total number who had preoperative potency.

to the urethra, thereby avoiding a vesical neck contracture, we have modified our technique by exteriorizing the bladder mucosa over the raw edges of the detrusor musculature (8). Recently, the role of the external sphincter mechanism has come under greater scrutiny, and we (9) have suggested that the autonomic innervation to the intrinsic skeletal muscle is important in ensuring urinary continence postoperatively. Of the 320 patients in this series who have been followed up for 1 year or longer, 296 (93%) are completely continent and wear no pads or appliances, and 21 (7%) have mild stress incontinence for which they wear a small pad in their trousers. No patient 1) is totally incontinent, 2) wears an external drainage device, or 3) has undergone placement of an artificial sphincter. The frequency of stress incontinence was similar in patients with stages A and B disease, which suggests that a prior transurethral resection of the prostate was not an important risk factor in patients with mild stress incontinence postoperatively.

Several authors have reported an improvement in results with urinary continence following adoption of this surgical technique. Fowler et al. (13) noted a reduction in total incontinence from 17% to 0% and occurrence of mild incontinence in only 4% of the patients. Similarly, O'Donnell and Finan (14) reported a reduction in total incontinence from 12% to 0%, with only 6% of the patients having mild stress incontinence. They also noted an increase in the functional urethral length and an increase in the peak urethral pressure profile with this technique, compared with their prior standard surgical approach. These data suggest that preservation of the pelvic nerves during radical retropubic prostatectomy plays a role in functional maintenance of urinary continence postoperatively.

PATHOLOGIC FINDINGS

The autonomic branches of the pelvic plexus to the corpora cavernosa (cavernous nerves) are located outside the capsule of the prostate and Denonvilliers' fascia; this is the first principle of this procedure. Thus if one knew that all tumors were intracapsular, it should be possible to preserve sexual function in all such patients without injury to these nerves. However, prostate cancer frequently penetrates the prostatic capsule into adjacent soft tissue. Thus a series of important interrelated questions will demonstrate whether preservation of sexual function compromises the removal of tumor. 1) Were the neurovascular bundles resected completely during standard radical prostatectomy in the past? 2) What are the pathologic findings and surgical margins compared with those of standard prostatectomy? 3) Does this technique provide local and distant control of disease?

The neurovascular bundles are located in the lateral pelvic fascia with the major tributaries of the dorsal vein of the penis and Santorini's plexus. During standard radical perineal prostatectomies, the lateral pelvic fascia was reflected off the prostate so that injury to the dorsal vein of the penis and Santorini's plexus could be avoided (6). Thus the excellent long-term control of disease that has been reported following radical perineal prostatectomy (control of local disease and distant metastases) has been achieved without routine resection of the lateral pelvic fascia and neurovascular bundles. Consequently, one must assume that the neurovascular bundles were damaged but not com-

pletely resected during radical perineal prostatectomy. Also, according to the descriptions of radical retropubic prostatectomy available in standard textbooks, there is no evidence that the neurovascular bundles were completely resected with the retropubic approach either (15,16). The neurovascular bundles are intricately attached to the rectum, and to resect them completely, one must dissect immediately and deliberately very close to the anterolateral and lateral surfaces of the rectum. Previously, this was not part of the surgical procedure. However, one of the great advantages of the anatomic approach to radical prostatectomy is the accurate control of blood loss, which provides a clear surgical field. With this technique, all structures are clearly visualized, and a deliberate decision can be made on the basis of the operative findings as to whether structures can be preserved or resected more widely with the specimen. Thus one can resect the entire neurovascular bundle (9,11) if necessary by dividing the fascia and enclosed neurovascular bundle lateral to the urethra and resecting the fascia lateral to the rectum (table 2). In this manner, a wider margin of resection can be achieved with this technique than was previously possible by blunt dissection.

Recently, we evaluated the pathologic specimens removed from the first 100 consecutive patients who underwent nerve-sparing radical retropubic prostatectomy (17). Although 41% of the patients had established capsular penetration, only 7 had positive surgical margins (17% with stage A disease; 18% with stage B2). These 7 patients had extensive periprosthetic involvement by tumor; 5 had involvement of the seminal vesicles, but in none were the surgical margins positive only at the site of the nerve-sparing modification. On the basis of these findings, our surgical pathologist saw no indication that the nerve-sparing modification compromised the adequacy of the removal of cancer, which was determined primarily by the extent of the tumor rather than the operative technique (17). Recently, we updated our results based on pathologic findings in 414 consecutive patients who had radical prostatectomies performed for clinical stages A and B cancer (table 3). Overall, 10% of the patients had positive surgical margins. The frequency of positive surgical margins was always equal to or less than the percent of patients with involvement of the

TABLE 2.—Percent of neurovascular bundles resected in 482 consecutive patients having radical retropubic prostatectomy^a

Clinical stage	No. of patients	Percent bundles resected ^b		
		++	+0	00
A1	21	81	19	0
A2	54	69	22	9
B1N	85	79	16	5
B1	220	61	35	4
B2	98	20	67	13
D0 ^c	4	50	25	25
Total	482	57	36	7

^a On the basis of clinical findings at surgery, neurovascular bundles were either preserved or partially or completely resected.

^b ++ = both neurovascular bundles preserved; +0 = 1 neurovascular bundle preserved; 00 = no neurovascular bundle preserved.

^c D0 indicates elevated acid phosphatase with no other evidence of metastatic disease.

TABLE 3.—Pathologic findings in 414 consecutive patients having radical prostatectomies

Clinical stage	No. of patients	Patients with pathologic findings, %				
		Confined to organ	Capsular penetration	Seminal vesicle involvement	Positive surgical margin	Positive lymph nodes
A1	16	94	6	0	0	0
A2	40	83	17	15	15	10
B1N	78	82	18	3	3	0
B1	196	65	35	10	9	3
B2	84	29	71	31	19	23
Total	414	64	36	13	10	7

seminal vesicles and similar to the frequency of patients with positive pelvic lymph nodes. This confirms our impression that patients with positive surgical margins have extensive disease and are in a high-risk category for development of distant dissemination.

Efficacy of this technique will be established only when long-term follow-up evaluations have been performed for determination of whether the control of local disease and distant metastases is similar to results achieved with standard radical prostatectomy. To aid in this comparison, we have been careful not to use adjuvant radiation therapy or hormonal therapy, so that we will be able to evaluate the true impact of radical prostatectomy alone on the control of prostate cancer. Of the 320 men who have been followed up for 1–5 years (table 1), 10 have developed distant metastases as their first sign of failure. All 10 had extensive tumor in periprostatic soft tissue, and 8 underwent excision of their neurovascular bundles. Five of the 10 patients had involvement of the seminal vesicles, and 2 had positive pelvic lymph nodes. Three other patients developed local recurrence as their first sign of treatment failure. Two patients had clinical stage B2 disease with extensive periprostatic involvement of soft tissue and positive surgical margins, and 1 patient with stage B1 disease had extensive periprostatic tumor with involvement of the seminal vesicles. Based on our experience with radical prostatectomy prior to the development of the nerve-sparing technique, we assumed that approximately 10% of the patients will develop local recurrence as the first sign of failure in the first 5 years postoperatively. Schellhammer (18) has also reported a 10% failure rate in the first 5 years in patients with clinical stages A and B disease. With longer follow-up in that group, the total failure rate increased to only 15%. Thus most local failures are seen within the first 5 years. We are monitoring this closely in our group of patients, but more time must elapse to determine whether the total local recurrence rate will exceed 10% (29 more patients) over the next 4 years.

COST OF SURGICAL CARE

The cost of medical care is an important and legitimate concern for all. Indeed, the total medical costs for the surgical treatment of prostate cancer have not been described well in the past. We have recently evaluated the total medical costs (preoperative consultation, total hospital bill, and professional fees) for 12 patients who underwent radical

retropubic prostatectomy with a 10-day hospital stay. The average total expense was \$9,000 (range, \$8,500–\$9,500). If the hospital stay were reduced to 7 days, this cost could be reduced by \$1,000. These medical expenses are comparable to the total charges for external-beam radiotherapy for the treatment of localized prostate cancer at this hospital, which average \$9,000.

FUTURE PROSPECTS

Radical prostatectomy, like other cancer operations, is best suited for patients with early localized disease. However, in the past, it was thought that the morbidity of this procedure was too high for the treatment of a disease that was detected so early in its onset and had a prolonged natural history when treated conservatively. Refinements in the surgical anatomy of the prostate have made possible the reduction of the morbidity of this operation. By reducing blood loss, a surgeon can perform a more meticulous operation with reduced blood transfusion requirements, improved visualization, wider excision of more advanced tumors than was previously possible, decreased frequency of pulmonary emboli, and improved sexual function and urinary continence postoperatively.

Because the morbidity of the procedure has been reduced, we can now offer this operation with confidence to a larger group of patients. Today it is clear that many patients with low-volume stage A disease may develop disease progression without treatment, and thus radical prostatectomy is a more acceptable option for exactly the same group of young patients who found it unacceptable in the past (19). Through the use of improved screening techniques such as ultrasonography, more patients with early localized prostate cancer can be identified. Furthermore, through the use of better staging techniques, including improved imaging and tumor markers such as prostate-specific antigen, those patients who are likely to benefit most from radical prostatectomy can be identified.

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IV. Adjuvant Therapy

Radiation Therapy as Adjuvant Treatment After Radical Prostatectomy

Paul H. Lange,* Pratap K. Reddy, Eitan Medini, Seymour Levitt, Elwin E. Fraley¹

ABSTRACT—Between 1977 and 1984, adjuvant radiation therapy was administered after radical prostatectomy to 71 patients at high risk for recurrence of carcinoma of the prostate. In 35 patients, tumor remained at the surgical margin (stage C2 disease) and/or the disease had invaded the seminal vesicles (stage C3). Thirty-six patients had microscopic metastases in the pelvic lymph nodes (stage D1a). Radiation therapy was administered only after full recovery from surgery, which included full recovery of continence. The average period between surgery and initiation of radiation therapy was 3 months. Serious or long-term complications attributable to irradiation occurred in 7% of the patients. Tumor recurred locally in only 2 patients. Five-year actuarial survival, disease-related survival, and disease-free survival for patients with stages C2 and C3 disease were 86%, 96%, and 80%, respectively. These survival values for patients with stage D1a disease were 74%, 90%, and 69%, respectively. Our results suggest a greater therapeutic benefit from radical prostatectomy and adjuvant radiation therapy than from radical prostatectomy alone for stages C2 and C3 disease or from radical prostatectomy alone or radiation therapy alone for stage D1a disease; however, the length of follow-up, number of patients treated, and problems in comparing our results with those from historical controls do not allow us to draw firm conclusions about the benefits of this combined therapy. Controlled, randomized studies clearly are required. The serum levels of prostate-specific antigen, but not prostatic acid phosphatase, were invariably elevated in patients at the time of clinical detection of disease recurrence and predicted recurrence up to 4 years before the event. Measurement of serum levels of prostate-specific antigen should be required in future studies of the efficacy of therapies for apparently localized carcinoma of the prostate.—NCI Monogr 7:141–149, 1988.

Radical prostatectomy after pelvic lymphadenectomy is an effective and increasingly popular treatment for patients with apparently localized carcinoma of the prostate (1). However, when this operation is applied broadly to such patients, pathologic analysis of resected tissue reveals that, in 25% to 50% of the men, the tumor has extended locally beyond the prostate (pathologic stage C), or has involved the pelvic lymph nodes (pathologic stage D1), or both (2–4). Many of these patients are at increased risk for local and

distant recurrence of the disease and need an effective adjuvant therapy. Over the last 10 years, we have conducted a phase I–II trial to test the efficacy of and tolerance of patients for adjuvant radiation therapy after pelvic lymphadenectomy and radical prostatectomy. Patients whose disease was upstaged after surgery to pathologic stage D1 or high-risk stage C were involved. We (5) have reported on patient tolerance and the early results for our patients at the VAMC in Minneapolis. In this article, we update the follow-up on these patients and report on several additional patients from the VAMC and from the UMHC.

METHODS

Adjuvant radiation therapy was begun in June 1977 at the VAMC and formally in January 1983 at the UMHC. All candidates for the therapy had undergone pelvic lymphadenectomy and radical prostatectomy. In all but 12, radical prostatectomies were performed by the retropubic approach. Before 1983, frozen sections of suspicious nodes were evaluated during surgery, and the procedure was terminated if tumor was detected. After 1983, in rare instances, radical prostatectomy was performed on a patient if one or two lymph nodes were visibly diseased but pathologic evaluation detected no further involvement. Therefore, in the majority of patients (94%), those with positive lymph nodes had microscopic disease only (i.e., stage D1a), and in this article all D1 patients are so designated.

During the surgery and after the prostate was removed, circumferential biopsies of the urethral and bladder neck anastomotic ends were submitted for frozen section analysis. If the biopsy specimens contained tumor, more tissue was excised and evaluated. This continued until the biopsies were negative or until it seemed that further excision would jeopardize postoperative continence. In the latter circumstances, the anastomosis was completed, and it was assumed that the patient would receive adjuvant radiation therapy. Biopsies were performed during surgery because after radical prostatectomy the short segment of membranous urethra attached to the prostate virtually disappears upon fixation, and pathologists often take tissue from the prostatic apex and call it the distal margin. Similarly, the margin of the bladder neck is often difficult for them to assess after fixation (3). Finally, after 1979, surgeons did not remove tissue lateral to the external iliac artery of most patients during pelvic lymphadenectomy so as to lessen their chances of postoperative leg edema (6).

After final pathologic analysis, adjuvant radiation therapy was considered for patients who had completely recovered from the operation. The pathologic staging categories given in table 1 were used. Because we think that capsular extension alone is a relatively less adverse prognostic parameter (7,8), stage C candidates for adjuvant radiation

ABBREVIATIONS: VAMC = Veterans Administration Medical Center; UMHC = University of Minnesota Hospital and Clinic; PAP = prostatic acid phosphatase; PSA = prostate-specific antigen.

¹ Departments of Urologic Surgery (P. H. Lange, P. K. Reddy, E. E. Fraley) and Therapeutic Radiology (S. Levitt), University of Minnesota Hospital and Clinic; and Urology Section (P. H. Lange, P. K. Reddy) and Therapeutic Radiology Service (E. Medini), Veterans Administration Medical Center, Minneapolis, MN.

* Reprint requests to: Paul H. Lange, M.D., Department of Urologic Surgery, University of Minnesota Hospital and Clinic, Mayo Memorial Bldg., Box 394, 420 Delaware St., S.E., Minneapolis, MN 55455-0321.

TABLE 1.—Pathologic staging categories

Stage	Category description
A1	Focal, well-differentiated cancer discovered incidentally after radical prostatectomy
A2	Incidentally discovered cancer that is diffusely distributed (>5% of the prostatectomy specimen) and/or a Gleason histologic grade higher than 6
B1	Palpable disease shown by pathologic evaluation to be confined to less than one lobe of the prostate
B2	Palpable disease shown by pathologic evaluation to involve one or more lobes
C1	Minimal perforation or penetration through the prostatic capsule but no tumor at the surgical margins
C2	Tumor at the surgical margins
C3	Invasion of seminal vesicles with or without other capsular extension
D1	Pathologically confirmed metastasis to the pelvic lymph nodes
D2	Clinical evidence of distant metastasis to bone or soft tissue

therapy were restricted to those with stage C2 or C3 disease. Men with pelvic lymph node involvement were considered for radiation therapy if they had 6 or fewer positive nodes. Each candidate also had to 1) present more than 1 month postoperatively, 2) be fully continent, 3) have a well-healed abdominal wound, and 4) have returned to approximately the same state of well-being as had existed preoperatively.

Radiation therapy was administered only at our 2 institutions. At the VAMC, it was delivered by a 4-million electron volt linear accelerator according to the following standardized protocol: For pathologic stage C disease, 60 Gy was delivered to the prostatic bed (including the urethral-vesical anastomosis) in 6½ weeks with a 4-field isocentric technique through ports averaging 10 × 10 cm. Patients with positive lymph nodes received 45 Gy in 5 weeks to the pelvis by anterior/posterior fields averaging 14 × 15 cm, after which the radiation to the prostatic bed was boosted to 60 Gy by a reduced 3-field technique averaging 10 × 10 cm anteriorly and 9 × 10 cm bilaterally.

At the UMHC, radiation was delivered by a 10-million electron volt linear accelerator. For pathologic stage C disease, 45 Gy was delivered to the prostatic bed through anterior and posterior fields of 12 × 12 cm. This was followed by a boost through 1 anterior and 2 lateral fields of approximately 10 × 10 cm and 9 × 10 cm, respectively, to bring the total dose to 60 Gy. In patients with positive nodes, the entire pelvis received 45 Gy through 15- × 16-cm anterior and posterior fields; prostatic boosts were then given through 3 fields to bring the total dose to 60 Gy.

After radiation therapy, all patients were followed at 3- to 6-month intervals for 1 year and then at 6-month intervals. Evaluation for distant recurrence included isotopic bone scans and serum PAP determinations. Local and pelvic recurrence was assessed by rectal examination and, when appropriate, by excretory urography or computed axial tomography. Disease-free status was confirmed in all appropriate patients in June 1987. No endocrine therapy was given until recurrence.

The PSA levels were retrospectively determined from frozen serum samples that had been obtained from many of the patients at their regular clinic visits and measured with the Tandem PSA assay (Hybritech Inc., San Diego, CA). For comparison, we also measured PAP levels from the same stored serum using the Tandem PAP assay (Hybritech Inc.). The upper limit of normal is 4 ng/ml for PSA and 3 ng/ml for PAP.

RESULTS

Of the patients who underwent radical prostatectomy before December 1984, we administered adjuvant radiation therapy to 71. At the VAMC, from June 1977 to December 1984, of the 199 patients who underwent radical prostatectomy, 37 had the appropriate pathologic stage C disease and 31 of these received radiation therapy. Of the 6 remaining patients, 2 refused therapy, 2 were lost to follow-up, and for 2 patients radiation therapy was ruled out to preserve postoperative potency. During the same period, 42 patients had stage D1 disease, 29 of whom received radiation therapy. Of the remaining 13 patients, 2 were lost to follow-up, 4 had more than 6 positive nodes, 2 were not totally continent, 1 had had a rectal perforation at surgery, 1 received radiation therapy elsewhere, and 3 refused therapy.

At the UMHC, the adjuvant radiation protocol was formally adopted in 1983. Before then, appropriate patients of only one of the authors (PHL) were irradiated (2 patients with stage C and 2 with stage D1a disease). In 1983 and 1984, 40 patients underwent radical prostatectomy at the UMHC; 9 had the appropriate pathologic stage C disease and 2 of them received radiation therapy. Of the remaining 7, 3 refused therapy, 1 was lost to follow-up, and 3 received radiation therapy elsewhere. Nine patients had stage D1 disease and 5 of them received radiation therapy. Of the 4 remaining patients, 1 had more than 6 positive nodes, 1 was not totally continent, 1 received radiation therapy elsewhere, and 1 refused therapy. At neither institution were any patients excluded from radiation therapy because of medical deterioration, recurrent tumor, or perioperative death.

The years the radical prostatectomies were performed for patients who received radiation therapy are presented in

TABLE 2.—Year of prostatectomy in patients participating in adjuvant radiation therapy trials

Stage	No. of patients								Total
	1977	1978	1979	1980	1981	1982	1983	1984	
C2 and 3	4	2	2	4	4	4	6	9	35
D1a	1	1	6	3	4	5	6	10	36
Total	5	3	8	7	8	9	12	19	71

TABLE 3.—Results of pathologic analysis of prostatectomy specimens

Pathology of specimens	Stage	
	C	D1a
Surgical margins only positive	11	12
Seminal vesicles only positive	4	5
Seminal vesicles positive and margins positive	18	16
Capsular penetration only	2 ^a	0
No capsule penetration, seminal vesicles negative	0	3
One node positive		14
Two to six nodes positive ^b		22

^a These 2 patients had substantial capsular penetration, a large volume of disease, and a pathologic grade >7 but no definite involvement of the surgical margins. For the purposes of analysis, these 2 patients are included in the margin-positive category.

^b Four of these patients had one or two visibly positive nodes at surgery, but for the purposes of this analysis they are included in the D1a category (microscopic involvement of pelvic lymph nodes).

table 2. Twenty patients with stage C and 20 with stage D1a disease received radiation therapy more than 5 years before this analysis, and all patients received radiation therapy at least 30 months before the June 1987 follow-up deadline. The median length of follow-up for patients with stage C disease was 51 months (range of 30 to 119) and for stage D1a it was 48 months (range of 8 to 113). Only 2 patients who received radiation therapy were lost to follow-up at 48 and 56 months after surgery, respectively. The median age of the patients was 64 years (range of 53 to 73).

The specific pathologic findings for patients with stages C and D1a disease who received radiation therapy are given in table 3. Sixty-three percent of the patients with stage C and 58% of those with stage D1a disease had seminal vesicle involvement. The prostatic specimens of all but 3 patients with stage D1a disease were pathologic stage C, and 61% had more than 1 positive node.

All but 2 of the patients who began radiation therapy completed the planned course. One patient suffered from severe nausea and vomiting and treatment was stopped at 52 Gy. The other patient developed a cutaneous herpes zoster infection in the irradiated field at 36 Gy and therefore therapy was discontinued. Neither patient had any subsequent sequelae and both were included in all analyses. The median interval between radical prostatectomy and the beginning of radiation therapy was 3 months and the range was 1 to 12 months. The reasons for a delay of more than 4 months were delayed wound healing in 3 patients, slow recovery of continence in 5, a postoperative stricture in 1, patient preference in 10, and scheduling errors in 6.

The complications of postoperative radiation therapy have been acceptable. During and immediately after treatment, many patients experienced diarrhea (32%), skin desquamation (14%), anal pain (4%), and dysuria and frequency (4%). For those with stage C disease, notable acute reactions included transient leg edema in 2 patients and a urinary tract infection in 1 patient. Only 3 patients with stage C disease had any complications after 6 months. One patient had a mild bladder neck stricture that was present before radiation therapy (but which became more severe after therapy) and required 3 dilations during 18 months.

Eventually, he was treated elsewhere by internal urethrotomy, after which he immediately became incontinent for the first time. An inflatable urethral cuff was inserted, and the patient remains continent after more than 5 years. One other patient suffered from prolonged constipation and another had irritable bowel syndrome; both conditions gradually resolved.

Among patients with stage D1a disease, 2 had significant acute symptoms of severe nausea and vomiting and a herpes zoster infection; they did not complete the planned course of therapy, as previously mentioned. Long-term complications among patients with stage D1a disease included significant unilateral leg edema in 1, for which he wears support stockings (this patient did not have the modified lymphadenectomy); a transient episode of hematuria in another; and persistent edema of the penis in 2 patients. No patients suffered from significant persistent dysuria or frequency, incontinence, other voiding difficulties, or rectal troubles. All patients were impotent after surgery (the potency-saving radical prostatectomy was only attempted in 3 of these patients, and none had had a return of erection at the time radiation therapy was begun). Seventeen patients requested a penile prosthesis; the prostheses were implanted without complications 6 months or more after completion of radiation therapy. In 5 patients, a trial of intracorporal drug injections to induce erections was initiated; in 2 of them the response was sufficient and they are maintaining potency by self-injection at home (9).

Disease has recurred locally in 2 patients who received postoperative radiation therapy. In 1 patient with stage C disease, local recurrence was detected at 35 months, and in another, who originally had stage D1a disease, local recurrence was detected simultaneously with distant metastasis at 81 months. Bone metastasis developed in 6 patients with stage C disease at 19, 26, 42, 60, 67, and 102 months, respectively, after surgery. All these patients initially had pathologically proven seminal vesicle involvement. All were treated with endocrine therapy; 3 have died of their disease 3, 19, and 24 months, respectively, after this treatment, and 6 died of unrelated causes 32, 33, 48, 67, 94, and 119 months, respectively, after surgery.

Among the 36 patients with stage D1 disease who received radiation therapy, distant metastasis occurred in 9 patients at 11, 12, 34, 36, 38, 42, 48, 62, and 81 months, respectively, after surgery. All men were treated with endocrine therapy, and 6 have either died of their disease or have been lost to follow-up 13, 24, 40, 48, 79, and 82 months, respectively, after this treatment. Five additional patients have died of unrelated causes 8, 33, 46, 58, and 91 months, respectively, after surgery.

To assess the effect of adjuvant radiation therapy on disease progression, we constructed actuarial curves for survival free of disease, total survival, and cancer-related survival by the Kaplan-Meier method (10). At 5 years, the disease-free survival was 80% for patients with stage C and 69% for patients with stage D1a disease (fig. 1). The 5-year total survival was 86% for patients with stage C disease and 74% for patients with stage D1a disease (fig. 2). Survival related only to deaths due to cancer (cancer-related survival) at 5 years was 96% for patients with stage C and 90% for patients with stage D1a disease (fig. 3).

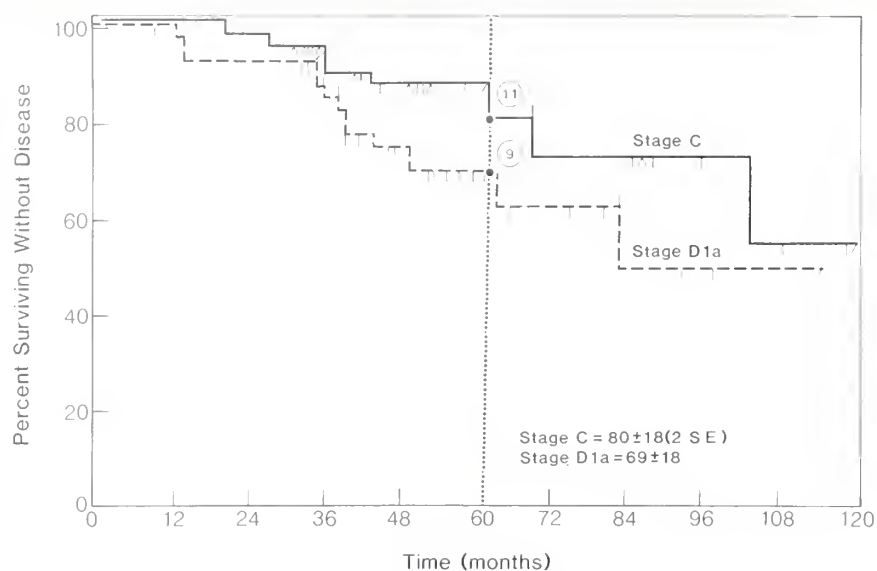


FIGURE 1.—Five-year, actuarial disease-free survival for patients with stage C and stage D1a disease. Encircled numbers represent patients at risk 60 mo after radical prostatectomy. Vertical lines represent censored data.

TABLE 4.—Number of patients with an elevated level of PSA before diagnosis of recurrence^a

Months before diagnosis	No. of patients with elevated PSA/total evaluated
0-5	3/3
6-11	7/7
12-17	3/4
18-23	3/5
24-29	4/6
30-35	2/4
36-41	— ^b
42-47	1/3

^a PSA was > 4 ng/ml.

^b No serum samples were obtained during this period.

A serum sample was taken at the follow-up visit at which a recurrence was determined clinically in 9 of the 17 patients whose disease recurred. In all 9, PSA was elevated (median of 100 ng/ml, range of 19 to 870 ng/ml), whereas PAP was elevated in only 3 (at 3, 15, and 47 ng/ml, respectively). Serum samples were available before the diagnosis of recurrence in 10 patients. The PSA, but never PAP, was elevated always at least 12 months before recurrence, and, in most patients, up to 36 months before recurrence and sometimes up to 4 years before recurrence (table 4). In 5 of these patients, the PSA values had returned to normal after radical prostatectomy and/or radiation therapy before becoming elevated; in the others, it could not be determined if PSA reached normal levels after surgery. Finally, among the patients who were free of disease at the last clinic visit, sera were available for 23; PSA (but not PAP) was elevated in 3 (15%).

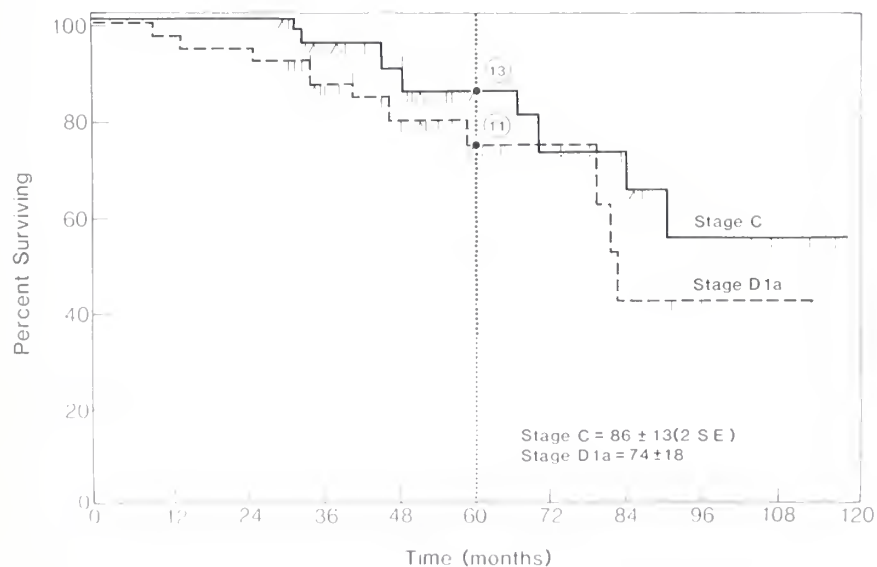


FIGURE 2.—Five-year, actuarial overall survival for patients with stage C and stage D1a disease.

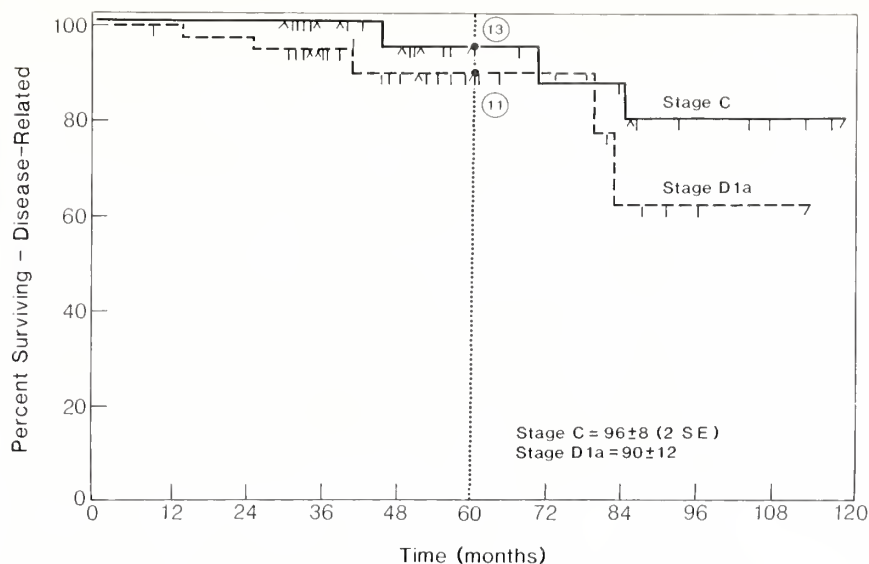


FIGURE 3.—Five-year, cancer-related survival for patients with stage C and stage D1a disease.

DISCUSSION

Pelvic lymphadenectomy followed by radical prostatectomy is becoming an increasingly popular therapy for apparently localized carcinoma of the prostate, in part because the morbidity, especially with regard to potency and incontinence, has been significantly reduced (*1,6,11*). However, when this therapy is applied to all appropriate patients whose disease is apparently confined to the prostate by rectal examination, a large percentage of them, after final pathologic staging, have disease outside the prostatic capsule, in the pelvic lymph nodes, or both (*2-4*). A great majority of these patients are at high risk for local or distant recurrence and need an adjuvant treatment.

There appears to be a wide spectrum of severity of disease labeled as pathologic stage C (*7,8*). Evidence is accumulating that the prognosis for patients with involved seminal vesicles is much worse than for those with no disease outside the prostate or for those with only capsular penetration (*7,12,13*). Also, patients with only positive surgical margins and no seminal vesicle involvement fare worse than those with capsular penetration but negative margins (*14*). Indeed, in our series and in those of others (*12*), most patients with documented metastases to the pelvic lymph nodes also have involved seminal vesicles and/or positive surgical margins and therefore may be at high risk for local recurrence (*3*). Thus we did not include pathologic stage C disease with only capsular penetration as a criterion for adjuvant radiation therapy. We made an exception to this criterion for 2 patients who had equivocally positive surgical margins but in addition had a large volume of tumor with a Gleason combined grade higher than 7.

One major theoretical choice for adjuvant therapy in patients at high risk for recurrence after radical prostatectomy is radiation therapy. Of course, radiation therapy is of no benefit to high-risk patients who already have systemic, albeit undetectable, disease after surgery. This might be true for a patient whose PSA level does not decline significantly after radical prostatectomy. However, we can assume that

at least some patients whose disease is upstaged to stage C2 or C3 after surgery have persistent though still only localized disease. It is likely that some residual disease is present in patients with positive surgical margins, especially if disease is at the anastomosis of the bladder neck and urethra. Also, an en bloc pelvic lymph node dissection for carcinoma of the prostate is not possible without removing the entire bladder. Thus tumor may commonly remain within the lymphatics. In such circumstances, radiation therapy may be efficacious because it seems to be curative as a primary treatment for some localized prostate cancers, especially if the volume of disease is small.

It is less likely that adjuvant radiation therapy is beneficial for patients with stage D1 disease. Many experts believe that most, if not all, patients with stage D1 have persistent disease beyond the pelvis at the time of surgery. This would seem to be the case for patients in whom there is evidence of recurrence a short time after surgery. Several studies have indicated that radiation therapy to the pelvis after only pelvic lymphadenectomy is of little benefit (*15,16*). Although patients with minimal stage D1 disease have survived 5 or more years, current data suggest that in most the disease recurs later (*17,18*). Even though such phenomena are consistent with occult distant metastasis at the time of radical prostatectomy, it is possible that some patients with stage D1 disease initially have only minimal persistent regional disease. This residual disease could serve as a source of subsequent systemic disease, and it might be sterilized by regional adjuvant radiation therapy. Thus we believed it was reasonable to test the therapeutic efficacy of adjuvant radiation therapy in these patients provided that the treatment was proved safe.

The safety of radiation therapy after radical prostatectomy has not been extensively studied. The results of some pertinent studies are listed in table 5. Ray et al. (*19*) administered adjuvant radiation therapy to 13 patients with stages C2 and C3 disease and to 19 patients who had locally recurrent disease. Radiation dose was usually more than 70 Gy. This therapy was considered safe, but the complications seemed significant: Five of 32 patients experienced

TABLE 5.—Safety of adjuvant radiation therapy after radical prostatectomy

Principal investigator	Reference	No. of patients	Chronic complications	Incontinence, %	Radiation to prostatic bed, Gy
Ray	(19)	32	16% severe	7	>70 ^a
Gibbons	(20)	22	14% severe	—	46–70
Pilepich	(21)	18	17% moderate/severe	6	≥65 (78%) ^a
Forman	(22)	16	38% total	13	65 ^a
Anscher	(23)	46	13%–20% severe	4	60–70 ^a
Present study		71	61% total	2 ^b	60 ^a

^a Most or all patients also received approximately 45 Gy to the pelvis.

^b One patient became incontinent after internal urethrotomy performed at another institution.

10 complications, which included exacerbation or onset of urinary incontinence (2), fecal incontinence (1), urethral stricture (2), rectal perturbations requiring colostomy (1), and leg edema (1). Gibbons et al. (20) observed severe complications in 3 of 22 patients who had undergone radical perineal prostatectomy and radiation therapy and in only 1 of 23 similar patients who did not receive radiation therapy. Complications after adjuvant radiation therapy included chronic proctitis and cystitis and rectal incontinence. One permanent colostomy and one urinary diversion were performed in this group of patients. All the complications occurred in patients given cobalt-60 in doses exceeding 65 Gy. Gill and associates (24) gave radiation therapy to 15 patients before and after radical prostatectomy. The total dosage was 75 Gy to the prostate and 50 Gy to the pelvis. Complications included stress incontinence in 40% of the patients and rectal injury at operation in 13%. Recently, Kaufman and co-workers (25) warned of the dangers of combined radiation therapy and radical prostatectomy and presented 4 patients in whom severe complications occurred. Only 1 of the patients received radiation therapy after radical prostatectomy, and the total dose delivered was more than 70 Gy. In Anscher and Prosnitz's (23) recent report on complications in 40 patients given adjuvant radiation therapy, those attributable to radiation included severe cystitis in 3 patients and incontinence in 1 patient. Pilepich et al. (21) and Forman and associates (22) also reported a similar incidence and severity of complications.

Our incidence of complications after radical prostatectomy and radiation therapy is low compared with many reports in the literature. Significant long-term complications occurred in 4 patients, but major surgery or a change in life-style was not required. This low incidence may partly reflect differences in reporting but may also be attributable to the following factors: 1) use of the modified lymphadenectomy technique to prevent leg edema; 2) limitation of dosage to 60 Gy; and 3) delivery of radiation therapy only after complete recovery from surgery, including recovery of continence. Radiation therapy given before radical prostatectomy is clearly fraught with more problems.

The effect of adjuvant radiation therapy on the incidence of local recurrence among our patients is difficult to assess. It is reassuring that disease has recurred locally in only 2 of 66 patients who had positive surgical margins, positive seminal vesicles, or both (table 3). However, in the absence

of an internal control group, we must judge the significance of our results by comparison with the literature. It is unfortunate that most of the numerous reports on this subject are either unclear or involve patients who are not comparable to ours. For example, many series included patients who also received endocrine therapy (26).

However, some reports on local recurrence after radical prostatectomy are pertinent to our series. The results of some of these series are listed in table 6. This subject was recently reviewed extensively by Robey and Schellhammer (26). Several important points emerge from a consideration of these series:

1) Local recurrence can often be ignored if the patient is asymptomatic or if it occurs simultaneously with the more symptomatic distant metastasis. After radical prostatectomy and radiation therapy, many patients have some rectal incontinence, which makes rectal examination less than totally accurate until disease is far advanced. Finally, the endocrine therapy for a distant metastasis attenuates the appearance of local progression.

2) The time until local recurrence is often prolonged. Jewett et al. (31) reported an interval of 6 months to 11 years to recurrence, whereas Culp (27) reported a median interval to recurrence of 4.5 years, although 15% of the recurrences were detected more than 15 years postoperatively. In a more recent series, Gibbons et al. (20) reported a median interval to recurrence of 51 months (range of 4 to 147). In 1 of our patients, the local recurrence was detected 81 months after surgery.

3) It appears that the final incidence of recurrence in long-term studies approaches 30%.

Perhaps in response to these local recurrence incidences, several investigators gave interstitial radiation therapy at the time of radical prostatectomy or external-beam therapy after surgery. Flocks and associates (32) used a radioactive colloidal gold solution interstitially during surgery and reported a low incidence of recurrence (4.4%) among 335 patients with clinical stage C cancer. A similar therapy was used more recently at the same institution by Rosenberg and co-workers (33). They treated 25 patients with stage C and 12 with stage D1a disease by pelvic lymphadenectomy, radical prostatectomy, and periprostatic radioactive gold seed implantation. With a median follow-up exceeding 45 months, local recurrence was observed in 2 of 25 patients with stage C and in 1 of 12 patients with stage D1a disease.

TABLE 6.—Local recurrence after radical prostatectomy

Principal investigator	Reference	Treatment ^a	No. of patients	Disease stage ^b	Recurrence, %	Follow-up, yr
Culp	(27)	RP	123	B	26	1-14
McCullough	(28)	RP	14	C	43	1-14
Tomlinson	(29)	RP	24	C	8	2-14
Walsh	(12)	RP	57	B	12	15
Zincke	(30)	RP	80	D1	14	3 (median)
Robey	(26)	RP	13	C	31	15
Gibbons	(20)	RP	23	C1-3	30	9 (mean)
		RP+RT	22	C1-3	5	
Pilepich	(21)	RP+RT	18	C1-3		
				D1	0	3.4 (median)
Forman	(22)	RP+RT	16	C1-3		
				D1	0	4 (median)
Present study		RP+RT	71	C2-3	3	2.5-10
				D1		

^a Treatment included: RP = radical prostatectomy; RT = external-beam radiation therapy.

^b All staging was pathologic, except that of McCullough and Leadbetter (28), which was clinical.

Several reports cite the incidence of local recurrence after radical prostatectomy and subsequent external-beam radiation therapy (table 6). For example, Gibbons et al. (20) reported a 5% incidence of local recurrence in 22 patients with stages C1 to C3 disease after a median follow-up of 9 years compared with an incidence of 30% in a similar, although nonrandomized, group of 23 patients who did not receive radiation therapy. Pilepich and co-workers (21) and Forman et al. (22) found no local recurrence among a group of patients with stage C or D1 disease, but follow-up was short in both reports. Others (19,23) also cite a low incidence of local recurrence, but some of the patients simultaneously received endocrine and radiation therapy.

Our incidence of recurrence after radical prostatectomy and radiation therapy seems lower than that reported after radical prostatectomy alone and similar to that reported after adjuvant radiation therapy. However, all the reported series were uncontrolled, and the number of patients and length of follow-up was not sufficient to ensure that radiation therapy definitely reduced the number of local recurrences. Nonetheless, postoperative radiation therapy has demonstrated benefit. It is safe. Also, regression of documented local postoperative recurrence has occurred with radiation therapy (19,22). Thus the fear of leaving some cancer at the anastomotic ends need not compel a surgeon to continue removing tissue at the risk of continence.

The 5-year actuarial survival free of disease among our patients with pathologic stages C2 and C3 disease was

80% after a median follow-up period of 51 months (range of 19 to 119). Although it was difficult to find reported data for patient groups comparable to ours, the reports by Gibbons and associates (20) and Zincke et al. (34) cited a 5-year disease-free survival of approximately 60% (table 7). Similarly, Middleton et al. (7) cited an actuarial 5-year survival in patients with positive seminal vesicles of 50%. Other reports on patients with pathologic stage C disease cited high 5-year, disease-free survival incidences of 70% to 82%, but many of the patients had capsular perforation only or did not undergo lymphadenectomy (35-37). Thus our 5-year disease-free survival of 80% for patients with stages C2 and C3 disease may be an improvement and indicate that postoperative radiation is beneficial. However, the 95% confidence intervals (± 2 SD) are broad ($\pm 18\%$) and overlap significantly with the reported figures for radical prostatectomy alone.

Our actuarial 5-year survival incidence for patients with stage D1a disease is 69% after a median follow-up of 48 months (range of 8 to 113). Again, comparisons with the literature are difficult, but reports on several series of patients with stage D1 cancer after radical prostatectomy seem comparable to ours. Zincke and Utz (30) reported on 51 patients with stage D1 disease and no treatment other than radical prostatectomy until progression. The 5-year actuarial survival free of disease was 18% overall and was slightly higher, at 26%, for patients with only one positive node. The mean interval to recurrence was 40

TABLE 7.—Five-year disease-free survival in patients with stage C disease after radical prostatectomy

Principal investigator	Reference	Treatment	No. of patients	Five-year survival		
				No evidence of disease, %	Disease stage	Follow-up, yr
Zincke	(34)	RP	80	60	C3	<5 (60%)
Middleton	(7)	RP	10	50	C3	5 (minimum)
Gibbons	(20)	RP	23	60	C1-3	9 (mean)
		RP+RT	21	71		
Present study		RP+RT	71	80	C2-3	4.3 (median)

TABLE 8.—Five-year disease-free survival after therapy in patients with stage D1 disease

Principal investigator	Reference	Treatment	Five-year survival		
			No. of patients	No evidence of disease, %	Follow-up
Zincke	(30)	RP	51	18	5 yr (mean)
Paulson	(15)	RP	11	?	18 mo (mean time to recurrence)
Smith	(16)	RT	25	35 (N1)	5 yr (minimum)
Bagshaw	(38)	RT	59	15	26–48 mo
Scardino	(17)	Gold-198, RT ^a	37	33 (N1)	4.5 yr (mean)
				7	8 yr
Present study		RP+RT	36	69	4 yr (median)

^a In addition to the radiation, the patients received gold-198 by interstitial implantation.

months. Paulson et al. (15) reported even more dismal results for patients with stage D1 disease, but they also observed that after radiation therapy or after no therapy other than lymphadenectomy the median time to recurrence was similar to that after radical prostatectomy. Thus it seems pertinent that we examine the reported incidence of disease-free survival for comparable patients with stage D1 disease who received only radiation therapy.

The results of several studies of patients with stage D1 disease who received radiation therapy are presented in table 8. Smith and Middleton (16) reported on 40 patients with only microscopic nodal disease after lymphadenectomy alone, 25 of whom also received radiation therapy. The actuarial 5-year survival free of disease was 35%, and radiation therapy did not appear to affect recurrence. Among 18 patients with only one positive node, the actuarial 5-year disease-free survival was 44%, but one-half of these patients developed a recurrence during further follow-up. Scardino et al. (17) reported similar survival rates for patients with minimal nodal disease (i.e., N1) after pelvic lymphadenectomy, interstitial gold implantation, and external-beam radiotherapy. The actuarial 5-year disease-free survival incidence for patients with limited microscopic nodal disease was only 33%, and this decreased significantly after 5 years: At 8 years the disease-free survival for patients with N1 disease was only 7%.

On casual observation, our actuarial 5-year survival incidence of 69% for patients with stage D1a disease seems to be an improvement over other reported results. Nevertheless, for a variety of reasons we believe the efficacy of adjuvant radiation therapy for stage D1a disease is unproved. Our 95% confidence levels are broad ($\pm 18\%$), and recurrences are being detected among our patients after 5 years. Finally, there is a wide spectrum of severity of stage D1 disease; it ranges from minimal microscopic disease to gross nodal involvement. Miller and Catalona (18) recently reported that 9 of 12 patients with very minimal nodal disease survived 5 years. In these patients, frozen sections showed apparently normal tissue, but some metastasis was detected in permanent sections. However, at 7, 9, and

10 years, the disease-free survival steadily decreased to 5 of 12, 4 of 9, and 1 of 3 patients, respectively (Catalona WJ: Personal communication). Thus it would appear that for both high-risk stage C and stage D1a disease randomized testing of the efficacy of adjuvant therapies is sorely needed.

An assay for serum PSA has recently become widely available, and many studies have now documented that this serum marker is extremely useful in monitoring patients with prostate cancer after initial therapies. Indeed, PSA is significantly superior to PAP in this regard. Elevated levels of PSA occur in over 95% of patients with stage D2 disease (39–42). More importantly, in those patients whose disease recurs after radical prostatectomy and adjuvant radiation therapy, PSA levels are often elevated for many years before a recurrence is manifest.² What therapeutic strategies may be exploited with this insight is unknown, but it is probable that disease-free survival analysis can use serum PSA levels to great advantage. For example, the time physicians need to evaluate therapies might be significantly reduced. Also, if the first unequivocal rise in PSA is used as the time to recurrence, the uncertainties of our pinpointing the time of recurrence might be reduced. If and when multi-institutional randomized studies of the value of adjuvant radiation therapy are begun, serum PSA determinations should be an essential part of patient evaluation.

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² The PSA levels after radical prostatectomy by the Hybritech assay are abnormal if ≥ 0.4 ng/ml (manuscript in preparation). Nonetheless, for this analysis, we used the traditional value of 4 ng/ml as the upper limit of normal.

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Chemotherapy for Prostate Carcinoma

Mario A. Eisenberger¹

ABSTRACT—We have evaluated the role of chemotherapy for the treatment of prostate carcinoma. The data of patients with endocrine-resistant stage D2 disease indicate that clinical benefits in such patients are at best marginal. Despite the controversies involved in the assessment of response in this disease, in this review we show that in over 3,000 patients eligible for evaluation, less than 10% had complete or partial responses to various treatment regimens. Survival evaluation on all prospective randomized clinical trials showed no advantages in favor of any treatment tested and, moreover, in 2 of such studies involving various single agents, survival was not better than a “no chemotherapy” control arm. Because of these data, we conclude that chemotherapy is not indicated as an adjuvant treatment for patients with localized prostate cancer. Although patients with prostate cancer frequently respond to androgen deprivation procedures, preclinical and clinical data strongly suggest the existence of endocrine-independent cell clones, which supports further testing with nonhormonal cytotoxic treatment. A close multidisciplinary interaction is a prerequisite for development of new effective systemic treatment in this disease.—NCI Monograph 7:151-163, 1988.

Our task for this important consensus development conference is to evaluate the role of nonhormonal cytotoxic chemotherapy as an adjuvant treatment for patients with localized prostate cancer. Although a significant proportion of patients with clinically localized disease can be cured or have their disease-free intervals prolonged by local modalities of treatment, most present with evidence of extracapsular tumor extension or disseminated disease, which generally implies incurability by these forms of treatment. Similarly, despite the increased sophistication of local forms of treatment and their widespread application, a significant proportion of patients initially approached with curative intent continue to die of metastatic cancer. Prostate cancer represents a prime model of endocrine-dependent tumors in males, and though most of the patients respond, both objectively and subjectively and sometimes dramatically, to a variety of androgen deprivation procedures, this effect is usually palliative and temporary. Most patients will eventually develop effective and irreversible resistance to this form of treatment in an almost predictable fashion. Current data support a biclonal origin of prostate cancer cells, which include both androgen-sensitive and -resistant cell clones (1-4). Resistance to endocrine manipulations in this disease may represent the expansion of previous insensitive clones, or a somatic mutation of sensitive cells, or both. In preclinical studies in various animal prostate tumor models,

the combined use of chemotherapy and endocrine ablation has been shown at times to be superior to either modality alone (5). Although extrapolation of data with nonhormonal cytotoxic treatment to other species (i.e., rat tumor models to humans) has not proved useful in this disease (5), both laboratory experiments and clinical data support the existence of an androgen-independent tumor growth phenomenon that provides a strong rationale for the application of nonhormonal chemotherapy in prostate cancer.

The evaluation of chemotherapy in prostate cancer is obscured by significant methodologic problems. Many of the difficulties are related to the disease itself. The most common metastatic site is in bone, manifested by diffuse sclerotic (osteoblastic) lesions that cannot be measured reliably to allow for assessments of therapeutic benefits. Serum markers, such as acid phosphatase, have not been shown to correlate well with the status of disease in most situations, and the evaluation of unidimensionally measured indicator lesions, such as prostate size by digital examination or radiologic methods, is controversial and is the subject of significant bias. Several response criteria that apply a variety of relatively imprecise and usually subjective parameters have been developed in the past, most of which are frequently the focus of significant criticisms (6-15). Despite these controversies, chemotherapy studies in this disease rely mostly on response rates as the primary evidence of therapeutic benefits.

Because of the unsettled nature of this problem, we attempted to determine the impact of chemotherapy on survival of patients with endocrine-resistant disease. We have analyzed all prospective randomized studies reported in the English literature over the past decades, focusing on survival as the main end point. We also provide a detailed description of results reported with a wealth of treatment regimens that have been primarily tested in patients with endocrine-resistant disease and indicate the specific response criteria used. These data represent the bulk of experience with chemotherapy in this disease and provide the background on which we base our recommendations with regard to its possible use in patients with localized disease.

UNCONTROLLED CLINICAL TRIALS

The data reported with single agents, including the response criteria utilized in individual studies, are illustrated in table 1. These studies should be carefully scrutinized because of their differences in criteria for evaluation, patient selection factors, and study design. In some instances, they represent broad trials including patients with various primary tumors in addition to prostate cancer (broad phase II trials), without disease-specific criteria for response, and frequently included insufficient numbers of patients in each

ABBREVIATION: NPCP = National Prostatic Cancer Project.

¹ Division of Medical Oncology, Department of Medicine, University of Maryland Cancer Center, 22 South Greene St., Baltimore, MD 21201.

TABLE 1.—Single-agent phase II trials with patients with hormone-resistant prostate carcinoma

Drug	Principal investigator	Reference	Total No. of responders/No. of patients eligible for evaluation	Response ^a		Improvement ^b	Response criteria
				Complete and partial	Stable disease		
Doxorubicin	O'Bryan	(16)	2/9	2	0	0	Broad phase II ^c
	O'Bryan	(17)	5/15	5	0	0	
	Torti	(18)	21/25	4 ^d	17	0	NPCP (13)
	Blum	(19)	7/51	NR	NR	NR	Not specified or unclear
	Scher	(20)	6/39	2	1	3(5)	MSKCC (6)
Carmustine	Carter ^e	(21)	2/15	NR	NR	NR	Not specified or unclear
Lomustine	Carter ^e	(21)	2/19	NR	NR	NR	Not specified or unclear
Cyclophosphamide	Carter ^e	(21)	8/57	NR	NR	NR	Not specified or unclear
Cisplatin	Yagoda	(9)	4/25	3	1	0(8)	MSKCC (6)
	Merrin	(22)	24/54	17	7	0(20)	Not specified or unclear
	Rossof	(23)	4/21	4	0	0	Broad phase II ^c
	Qazi	(24)	0/17	0	0	0	Standard for solid tumors, decrease in markers
	Moore	(25)	3/29	0	0	3 ^f	Standard for solid tumors, decrease in markers
Estracyt	Mittleman	(26)	9/44	9	0	0(7)	NPCP (13)
	Fosså	(27)	6/17	NR	NR	6(3)	Not specified or unclear
	Jonsson	(28)	28/91	NR	NR	28(24)	Not specified or unclear
	Kuss	(29)	3/15	3	0	0(2)	Not specified or unclear
	Leistenschneider	(30)	8/23	NR	NR	8(10)	Not specified or unclear
	Edsmyr	(31)	19/90 ^g	NR	NR	NR(49)	Not specified or unclear
	Nilsson	(32)	28/91	NR	NR	NR(24)	Not specified or unclear
	Veronesi	(33)	20/27	3	17	0	NPCP (13)
5-Fluorouracil	Moore	(34)	7/7	4	3	0	Broad phase II ^c
	Ansfield	(35)	1/7	0	0	NR	Broad phase II ^c
	Weiss	(36)	1/4	NR	NR	NR	Broad phase II ^c
	Hall	(37)	3/6	NR	NR	NR(3)	Broad phase II ^c
Hydroxyurea	Lerner	(38)	19/30	15	4	0	Not specified or unclear
Mithramycin	Kofman	(39)	2/6	NR	NR	NR	Broad phase II ^c
	Carter ^e	(21)	2/36	NR	NR	NR	Not specified or unclear

disease category. Table 1 also includes broad reviews of multiple studies and specific aspects.

These basic differences in methodology account for a disturbing variability in response reported with the same agent by a different investigator. For example, as reported by O'Bryan et al. (16,17) and Torti and associates (18), doxorubicin appeared to have significant activity. However,

use of stricter criteria for evaluation in patients with bidimensionally measurable disease, as tested by Scher and co-workers (20), resulted in disappointing response rates, e.g., 2 of 39 patients had partial responses (5%, 95% confidence interval 0%–12%). Similar experience was reported with single agents, such as cisplatin, 5-fluorouracil, and estramustine phosphate (see table 1). Several of these

TABLE 1.—Single-agent phase II trials with patients with hormone-resistant prostate carcinoma (*continued*)

Drug	Principal investigator	Reference	Total No. of responders/No. of patients eligible for evaluation	Response ^a		Improvement ^b	Response criteria
				Complete and partial	Stable disease		
Mitomycin	Humphrey	(40)	0/4	0	0	0(4)	Broad phase II ^c
Melphalan	Houghton	(41)	1/15	0	0	1(1)	Not specified or unclear
Nitrogen mustard	Karnofsky Carter ^e	(42)	0/3	0	0	0(2)	Broad phase II ^c
		(21)	12/31	NR	NR	NR	Not specified or unclear
Prednimustine	Catane	(43)	5/23	0	0	5(8)	Not specified or unclear
Vincristine	Carter ^e	(21)	2/22	NR	NR	NR	Not specified or unclear
<i>m</i> -Amsacrine	Drelichman Natale	(44)	10/21	0	10	0	NPCP (13)
		(45)	0/19	0	0	0	MSKCC (6)
Aziridinybenzoquinone	Nichols	(46)	16/36	0	13	3	Broad phase II ^c
Dihydroxyanthracenedione	Drelichman	(47)	7/35	2	5	0	Not specified or unclear
Hexamethylmelamine	Drelichman	(48)	0/14	0	0	0	NPCP (13)
Mitoguazone	Scher Moore	(49)	6/29	6	0	0(3)	MSKCC (6)
		(50)	0/19	0	0	0	Standard for solid tumors, decrease in markers
Neocarzinostatin	Natale	(51)	0/14	0	0	0	MSKCC (6)
Vindesine	Jones	(52)	16/27	5	11	0	Standard for solid tumors, decrease in markers
VP-16-213	Nissen Walther	(53)	2/5	1	0	1	Broad phase II ^c
		(54)	1/23	1	4	0	Standard for solid tumors, decrease in markers
Spirogermanium	Dexeus	(55)	0/13	0	0	0	Logothetis et al. (14)

^a NR = not reported or responses reported but not quantitatively classified as complete or partial, stable disease, or improvement; MSKCC = Memorial Sloan-Kettering Cancer Center.

^b Improvement indicated objective evidence of response but less than a partial response. Values = numbers of patients; *values in parentheses* indicate subjective improvement.

^c Broad phase II indicates that no specific criteria were listed or description was unclear.

^d Patients (4 of 12 with complete and partial responses) had bidimensionally measurable disease.

^e Work was a review of multiple dose schedules.

^f All 3 patients had normalization of acid phosphatase levels only; 9 patients with measurable disease had no regression of tumor.

^g Numbers included 26 of 90 patients with no prior hormonal treatment. Actual results for patients with hormone-resistant disease are unclear.

agents alone and in combination were subsequently tested in prospective randomized trials with discouraging results, despite preliminary evidence of antitumor activity derived from phase II studies. This divergence of results and lack of reproducibility are not unique to prostate cancer, but these data illustrate that they are particularly prevalent in this disease. Despite these difficulties, the data illustrated with the various single agents in table 1 suggest that their antitumor activity is at best marginal and of limited clinical significance.

Table 2 illustrates the data available with various drug combinations tested in prostate cancer therapy. Not surprisingly, combinations of agents with modest activity have not yielded satisfactory results.

RANDOMIZED CLINICAL TRIALS

Because current standard methodology of clinical drug testing looking at response rates as the major study end point is not feasible for the majority of patients with prostate

TABLE 2.—Phase II trials with combination chemotherapy

Drug combination	Principal investigator	Reference	Total No. of responders/No. of patients eligible for evaluation	Response ^a		Improvement ^b	Response criteria
				Complete and partial	Stable disease		
Cyclophosphamide + doxorubicin	Izbicki	(56)	8/20	3	5	(8)	Standard for solid tumors, decrease in markers
	lhde	(8)	11/22	7	4		See (8)
	Merrin	(57)	5/19	0	5	(8)	Not specified or unclear
	Lloyd	(58)	2/11	2	0		Broad phase II
	Soloway	(59)	12/21	0	12	(5)	NPCP (13)
Cyclophosphamide + 5-fluorouracil	Merrin	(57)	2/13	1	1	0(7)	Not specified or unclear
Estramustine phosphate + 5-fluorouracil	Kennealey	(60)	3/25	0	0	3(8)	Not specified or unclear
Chlorambucil + prednisolone	Beckley	(61)	2/11	0	2	0	NPCP (13)
Carmustine + cyclophosphamide + doxorubicin	Presant	(62)	11/27	7	4	2	Standard for solid tumors, decrease in markers
	Citrin	(63)	10/21	NR	NR	NR	See (63)
Doxorubicin + cisplatin	Perloff	(64)	9/17	9	0	(2)	Not specified or unclear
	Anderson	(65)	7/83	NR	NR	7(55)	Not specified or unclear
Cyclophosphamide + doxorubicin + cisplatin	Seifter	(66)	7/21 ^c	7	6	0	See (8)
Cyclophosphamide + cisplatin + prednisone	Berry	(67)	10/22	0	10	0	NPCP (13)
Doxorubicin + 5-fluorouracil + mitomycin	Logothetis	(14)	30/62 ^d	NR	NR	NR	See (14)
	Kasimis	(68)	7/16	0	7	0(9)	NPCP (13)
	Hsu	(69)	9/14	1	8	0(10)	NPCP (13)
Melphalan + methotrexate + 5-fluorouracil + vincristine + prednisone	Paulson	(70)	51/84 ^e	3 ^f	0	NR(40)	See (70)
Cyclophosphamide + methotrexate + 5-fluorouracil + vincristine + prednisone	Buell	(71)	6/16	5	1	(11)	Standard for solid tumors, decrease in markers

^a See footnote a, table 1.^b See footnote b, table 1.^c All stage D2 patients were treated before initiation of endocrine treatment. Sites and types of response are unclear.^d Responses were seen in 18 of 41 patients with bone metastasis only and 12 of 21 with bone and visceral sites (8 in the lung).^e Twenty-four patients had at least a 50% decrease in acid phosphatase, 13 had normalization, and 11 had a 50% reduction without normalization.^f Three of 7 patients with bidimensionally measurable disease had complete and partial responses.

carcinoma, evaluation of survival, independent of response status, in prospective trials may be fundamental to the evaluation of treatment efficacy in this disease. The evaluation of survival in phase II studies, in which the survival of responders versus nonresponders is compared, is not a valid method of assessment of therapeutic efficacy (72).

Investigators involved in the NPCP have evaluated several chemotherapeutic agents in a series of prospective randomized studies in hormone-resistant patients (table 3). On their initial 2 trials, NPCP investigators tested various chemotherapeutic agents against a standard treatment control arm. Standard treatment represented a group of

TABLE 3.—Randomized trials for prostate carcinoma: NPCP studies

Study No.	Reference	Treatment	No. of patients eligible for evaluation/No. entered	Response		Survival, wk ^a
				Complete and partial	Stable disease	
100	(73)	Cyclophosphamide	41	4	20	47
		5-Fluorouracil	33	4	14	44
		Standard ^b	36	0	7	38
200	(74)	Estramustine phosphate	46/54	3	11	26
		Streptozocin	38/46	0	12	25
		Standard ^b	21/25	0	4	24
300	(75)	Cyclophosphamide	35/39	0	9	27
		Dacarbazine	55/68	2	13	40
		Procarbazine	39/58	0	5	31
400	(76)	Estramustine phosphate + prednimustine	54	1	6	37
		Prednimustine	62	0	8	36
700	(77)	Cyclophosphamide	43/47	3	12	41
		Semustine	27/38	1	7	22
		Hydroxyurea	28/40	2	2	19
800	(78)	Estramustine phosphate	27/38	1	6	26
		Vincristine	29/42	1	4	22
		Estramustine phosphate + vincristine	4/41	0	7	32
1100	(79)	Estramustine phosphate	50/63	1	16	43
		Methotrexate	58/67	3	21	37
		Cisplatin	50/59	2	16	33
1200	(80)	Estramustine phosphate	40/50	0	7	38
		Cisplatin	42/51	0	9	28
		Estramustine phosphate + cisplatin	42/48	0	14	40

^a Median survival was calculated for all studies except study 400.

^b Standard therapy consisted of radiation, prednisone, chlorotrianisene, dexamethasone, testosterone, diethylstilbestrol, stilphostrol, spironolactone, cryosurgery, dicorvin, or Estinyl.

patients randomly allocated to receive various palliative measures including radiation therapy and/or alternative hormonal approaches such as corticosteroids, chlorotrianisene, testosterone, diethylstilbestrol, stilphostrol, aldactone, dicorvin, and Estinyl. For their first study (NPCP 100), patients were randomized to receive 1 of the single agents, i.e., cyclophosphamide, 5-fluorouracil, or standard treatment (73). In their second study (NPCP 200) for patients who had received pelvic radiation (≥ 20 Gy) previously, the random allocation included streptozocin, estramustine phosphate, or standard treatment (74). Based on higher percentages of responses (complete and partial responses and stable disease) observed on the chemotherapy arms in both studies compared with standard treatment, researchers concluded that chemotherapy was superior to standard treatment. This served as the background for further testing of various single agents and combinations in a similar fashion. The NPCP studies include stabilization of disease in their response criteria as a reflection of therapeutic benefits. According to the group's definition, stable disease reflects no evidence of progression for 12 weeks. Patients with stable disease have a median survival comparable to those classified as achieving a partial response by their criteria and

have a longer survival than do those with evidence of progression during this interval (13). However, what remains unproved is whether stable disease resulted from treatment. It may be logical for one to assume that patients with more aggressive disease demonstrating objective progression during the first 12 weeks of treatment live shorter lives than do those with a more indolent biology, but without evidence of progression during that same interval. Thus, because it remains possible that stabilization is a function of the disease itself rather than treatment, its inclusion is not acceptable and may inflate response rates falsely. Of the 79 "responders" in studies 100 and 200, only 11 (14%) could be classified as objective responders, i.e., had complete and partial responses, whereas the remaining 68 (86%) were included in the stable disease category. Survival results (fig. 1 and 2) indicated no differences among the various study arms (81). These results would indicate that chemotherapy has not been shown to be superior to standard treatment and that a "no chemotherapy" treatment continues to be the most appropriate control arm with which new treatments should be compared (table 3, fig. 1-3).

Several other groups conducted additional randomized studies in endocrine-resistant patients, and these are shown

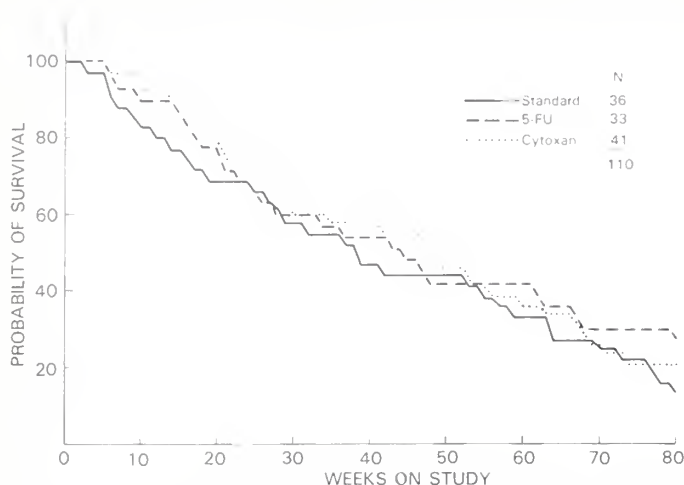


FIGURE 1.—NPCP Protocol 100: Probability of survival for randomized treatment groups.

in table 4 and figure 4. Like the NPCP studies, these other trials failed to demonstrate a clear superiority of one treatment regimen over another. Figure 5 illustrates the similarities between survival curves observed with various treatment programs tested in prospective randomized clinical trials including 20 or more adequately treated patients per arm. It also stresses the point that survival of patients with endocrine-resistant prostate carcinoma entering chemotherapy clinical trials is short and limited to a few months.

DISCUSSION

We described the overall experience with chemotherapy in prostate cancer. Because reproducible measures of antitumor effects are usually lacking, the conduct of phase II studies for screening new agents is mostly unsatisfactory. We have analyzed the randomized clinical trials focusing on survival as the main end point, and the data on all such studies reported in the English literature indicate that in no instance was any treatment program proved superior to another. Furthermore, in 2 studies conducted by the NPCP, the evaluation of 4 chemotherapeutic agents (cyclophosphamide, 5-fluorouracil, estramustine phosphate, and streptozocin) did not result in any prolongation of survival compared with a no chemotherapy control arm (standard treatment). Regardless of the controversies associated with response criteria, of the 3,184 patients treated with the various regimens illustrated in this review, only 202 (6.5%) satisfied the criteria for a complete or partial response. Four hundred eighty-five patients (15%) had stabilization of disease at 12 weeks that cannot be interpreted as a beneficial drug effect.

We have focused on the difficulties involved in testing chemotherapeutic agents in the treatment of this disease, stressing various methodologic aspects inherent to the clinical presentation of prostate carcinoma. An equally important factor relates to the patient population usually referred for treatment in clinical trials with cytotoxic drugs. Such patients have far advanced disease and present with a multitude of debilitating symptoms reflected by their limita-

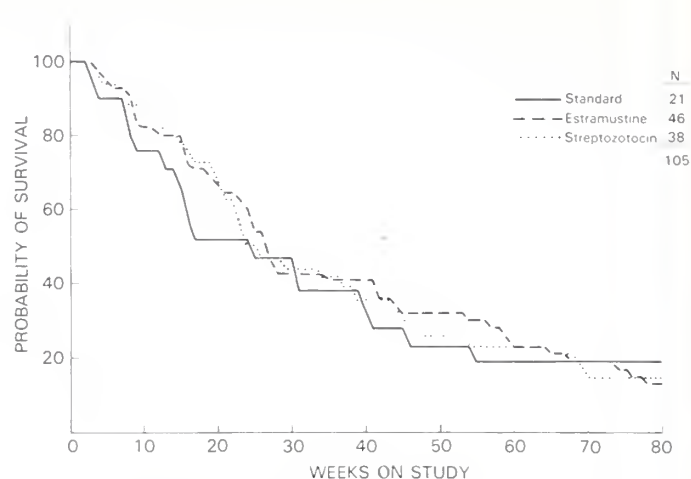


FIGURE 2.—NPCP Protocol 200: Probability of survival for randomized treatment groups.

tions in performance status and poor tolerance to therapy. The lack of hematologic tolerance in these patients is primarily due to widespread bone marrow replacement by tumor and is frequently aggravated by prior palliative radiation therapy to marrow-harboring areas; these two aspects result in signs and symptoms of adverse prognostic significance (91). Such aspects undoubtedly limit the chances for a more favorable response to treatment and may at least partially account for the refractory nature of this disease. Similarly, it remains possible that the mechanisms involved in the development of resistance to endocrine and cytotoxic chemotherapy in prostate cancer have common elements and that failure with one modality of treatment reflects resistance to the other.

Several investigators have reported attempts to test chemotherapy in conjunction with standard endocrine approaches or prior to such treatment. As previously mentioned, current data support a biclonal origin of prostate cancer cells that includes both androgen-dependent and -independent clones (1-4). This hypothesis offers an attractive rationale for testing nonhormonal cytotoxic treatment with conventional endocrine manipulations. Most randomized studies in which a combined chemohormonal therapy is tested against hormonal therapy alone have been done with either cyclophosphamide or estramustine phosphate (92-94). This latter compound (a conjugated estradiol derivative and mechlorethamine linked to carbon 3 of the steroid) was tested either alone, in combination with a standard endocrine treatment, or with cyclophosphamide. None of the studies reported thus far has shown a clear-cut advantage of responses, time to progression, and survival for combined approaches compared with standard endocrine treatment (92-94). However, this method of study may be the most appropriate way for further development of newer agents that demonstrate preliminary evidence of antitumor activity in phase II studies. Figure 6 illustrates the survival curves of NPCP studies 500 and 600.

The administration of exogenous testosterone for priming prostate cancer cells and increasing their susceptibility to chemotherapy has also been explored (95-97). In a relatively small randomized study, patients with endocrine-

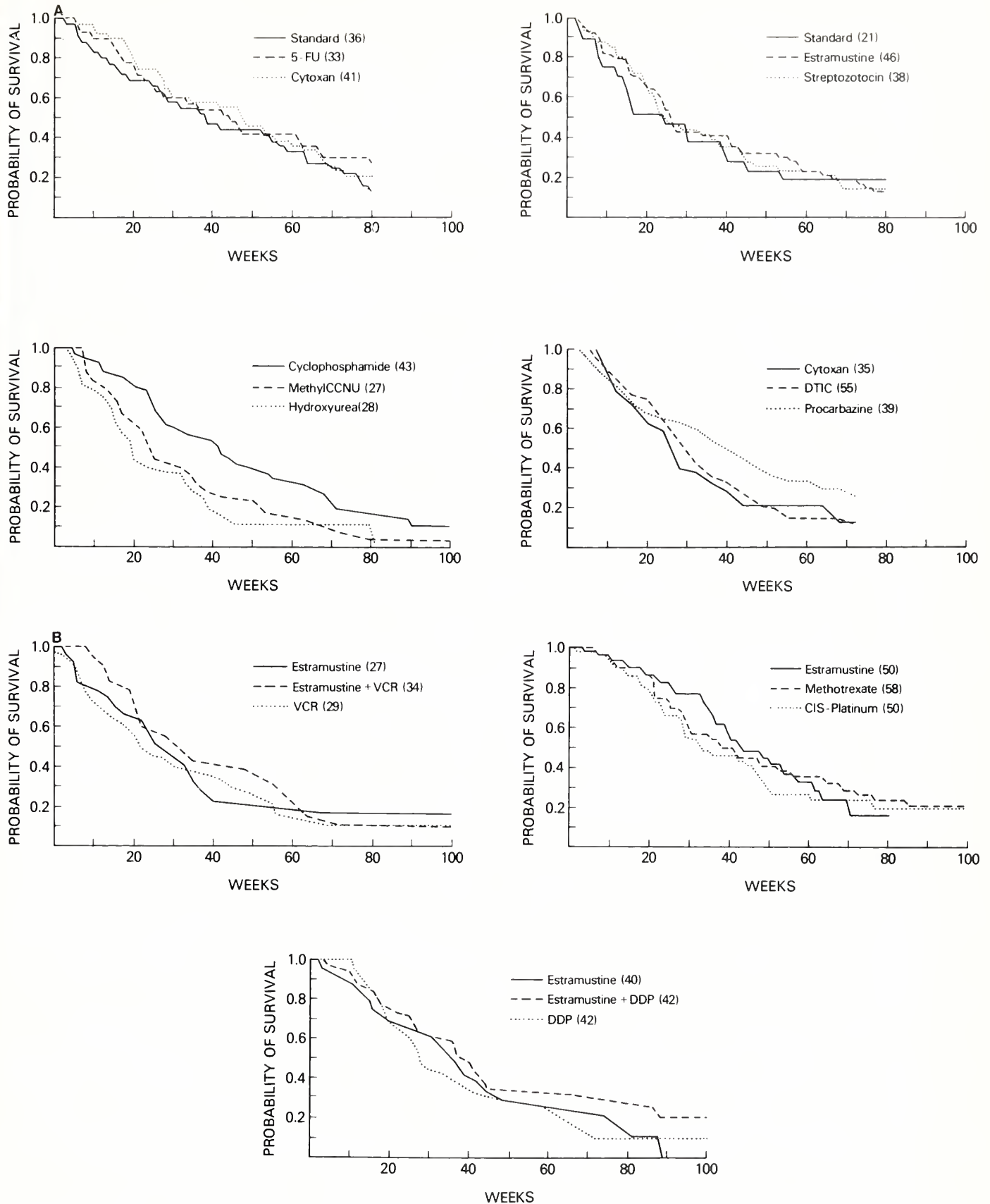


FIGURE 3.—Probability of survival in NPCP randomized studies. 5-FU = 5-fluorouracil; methylCCNU = semustine; DTIC = dacarbazine; VCR = vincristine; CIS-Platinum = cisplatin; DDP = cisplatin.

TABLE 4.—Other randomized trials with drug therapy for patients with prostate carcinoma^a

Drug and/or combination	Principal investigator	Reference	No. of patients eligible for evaluation/No. of patients entered	Response		Median survival ^b	Response criteria ^c
				Complete and partial	Stable disease		
5-Fluorouracil	Smalley	(82)	32/49	2	5	34 wk	<i>See</i> (82)
Cyclophosphamide + doxorubicin + 5-fluorouracil			39/52	2	4	25 wk	
Adriamycin	Eagan	(10)	19	—	—	NR	Ancillary scoring system [including crossed-over patients (10)]
Cyclophosphamide + 5-fluorouracil			18	—	—	NR	
Cyclophosphamide	Chlebowski	(83)	15	0	8	7.2 mo	NPCP (13)
Cyclophosphamide + doxorubicin + 5-fluorouracil			12	0	6	8.9 mo	
Cyclophosphamide	Muss	(84)	17	0	9	8 mo	NPCP (13)
Cyclophosphamide + methotrexate + 5-fluorouracil			15	1	7	5 mo	
Cyclophosphamide + methotrexate + 5-fluorouracil	Herr	(85)	20	3	4	26 wk	Standard for solid tumors, decreased acid phosphatase
Lomustine			20	0	6	24 wk	
5-Fluorouracil	Tejada	(86)	8	2	1	NR	Standard for solid tumors, decreased acid phosphatase
Lomustine			10	4	2	NR	
Doxorubicin	Pavone-Malacuso	(87)	11/22	0	3	NR	NPCP (13)
Procarbazine			14/24	1	0	NR	
Doxorubicin	DeWys	(11)	96/112	15/61 ^d	0	29 wk	Standard for solid tumors, decreased acid phosphatase
5-Fluorouracil			51/54	3/42 ^d	0	24 wk	
Cyclophosphamide + doxorubicin	Stephens	(88)	68	6/19 ^d	18	27 wk	Standard for solid tumors, decreased acid phosphatase
Hydroxyurea			69	1/24 ^d	9	28 wk	
Doxorubicin	Torti	(89)	20	1/13 ^e	8	48 wk	<i>See</i> (89)
Doxorubicin + cisplatin			17	2/10 ^e	9	43 wk	
Cyclophosphamide	Kasimis	(90)	16	0	8	7.9 mo	NPCP (13)
5-Fluorouracil + doxorubicin + mitomycin			14/15	1	5	8.9 mo	

^a Improvement was reported but not quantitated or some evidence was given that was regarded as a treatment benefit, e.g., decrease in marker values or decrease in prostate size, by most investigators. Eagan et al. (10) reported improvement in 5 patients given Adriamycin and 2 with the combination therapy.

^b NR = not reported.

^c Criteria used were the same for both trials.

^d Only values for patients with measurable disease are given, including those with bidimensionally measurable disease, elevated markers, or with bony lesions that could be evaluated. Values include crossed-over patients.

^e Objective responses are recorded separately according to their category of measurable versus those with evaluation potential. Ancillary responses included regarding improvement do not allow for a determination of an actual denominator.

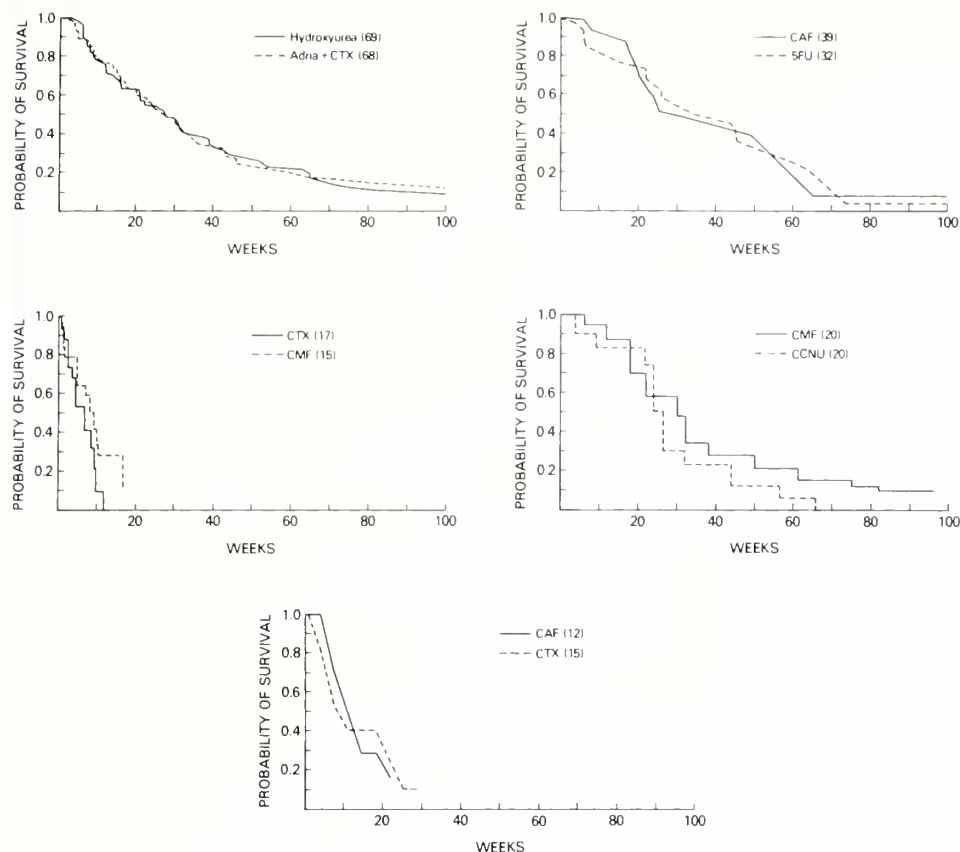


FIGURE 4.—Probability of survival in other randomized studies. Adria = doxorubicin; CTX = cyclophosphamide; CAF = cyclophosphamide, doxorubicin, 5-fluorouracil; 5FU = 5-fluorouracil; CMF = cyclophosphamide, methotrexate, 5-fluorouracil; CCNU = lomustine.

resistant disease were treated with a combination of drugs with or without prior stimulation with exogenous androgens; preliminary results indicated no advantages for this new approach (97). These negative preliminary findings may be explained by the lack of effective chemotherapy for this disease and by the fact that the investigators chose to test this concept in patients with endocrine-resistant disease, who may not be susceptible to exogenous androgenic stimulation. Additional studies are necessary if we are to determine optimal ways to combine chemotherapy and hormonal treatment.

Seifter et al. (66) recently reported their preliminary results with the combination of cyclophosphamide, doxorubicin, and cisplatin in newly diagnosed stage D2 patients before they were given endocrine treatment. Although their results with cytotoxic treatment were essentially negative, it

appeared that such an approach did not prevent subsequent responses to endocrine treatment, which suggests that chemotherapy does not change the biology of prostate cancer relative to its sensitivity to androgen deprivation procedures. This approach is ethically justifiable because delaying endocrine treatment for stage D2 patients until they become symptomatic has not been shown to affect survival adversely (98-101). Patients with newly diagnosed

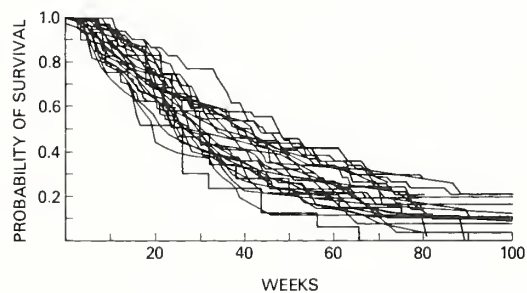


FIGURE 5.—Composite figure of survival curves of treatments with 20 or more patients who could be evaluated per arm.

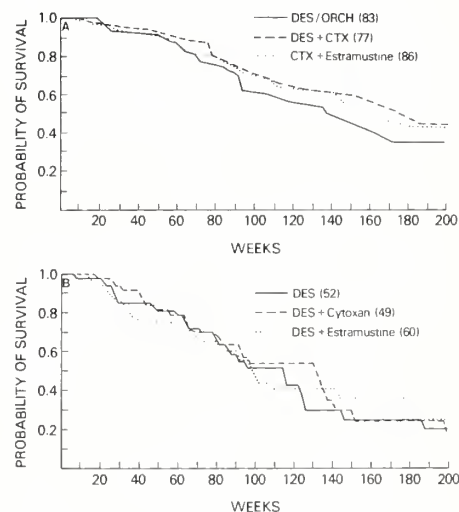


FIGURE 6.—Chemotherapy and hormonal therapy used in NPCP studies 500 (A) and 600 (B). DES/ORCH = diethylstilbestrol/orchiectomy.

stage D2 disease may be a more suitable group for testing new drugs because they have less extensive disease, better performance status, less prior treatment, and more frequently present with evidence of measurable soft tissue disease.

The selection of patients with bidimensionally measurable disease for new drug development has been the subject of significant criticism. These patients are considered by many as a subgroup with distinct biologic features and not representative of the usual patients with prostate cancer presenting with bone metastasis only. However, this has not been substantiated by any solid clinical evidence. Patients with soft tissue metastases respond well to first-line endocrine treatments and frequently demonstrate marked regression of measurable disease. Data on file at the Southwest Oncology Group (Blumenstein B, Crawford ED: Personal communication) of patients with endocrine-resistant prostate cancer who entered various chemotherapy studies indicate that time-to-treatment failure and survival are the same for patients with measurable disease versus bone disease only. At present, we favor the conduct of phase II studies with patients with reproducible evidence of bidimensionally measurable disease. Whereas this approach allows for a more reliable assessment regarding the preliminary activity of new agents, it is frequently confounded by the fact that even in this situation the dominant site of disease is still in bones, thus potentially providing fragmentary evaluation of the patient. Because of this, we suggest that more definitive evidence of therapeutic efficacy should derive from phase III studies in which survival is the main study end point. Because results with chemotherapy have thus far been generally disappointing, the most appropriate control with which new treatments should be compared continues to be a no chemotherapy arm, consisting of a uniformly applied second-line, endocrine manipulation, or symptomatic care.

In summary, we have described and discussed the extensive experience with chemotherapy for prostate cancer. The results indicate that, regardless of the controversies, the clinical benefits associated with this form of treatment have been marginal and that routine use of this modality should be reserved to an investigational setting or for the clinical situation in which other forms of less toxic palliative treatments have failed. At this time, there is no indication that cytotoxic chemotherapy is likely to provide additional benefits for the treatment of patients with localized prostate cancer.

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Hormone Therapy for Prostate Cancer: Results of the Veterans Administration Cooperative Urological Research Group Studies¹

David P. Byar,* Donald K. Corle²

ABSTRACT—Between 1960 and 1975, the Veterans Administration Cooperative Urological Research Group conducted a consecutive series of 3 major randomized clinical trials comparing various endocrine treatments for newly diagnosed prostate cancer patients. Six major conclusions concerning hormonal treatment emerged from these studies: 1) increased hazard of cardiovascular death after therapy with 5 mg diethylstilbestrol (DES); 2) orchiectomy plus DES no better than orchiectomy or DES alone; 3) equivalent effect of 1.0 and 5.0 mg DES on cancer; 4) reduced cardiovascular hazard from therapy with 1.0 mg DES; 5) Premarin and Provera no better than 1.0 mg DES at doses studied; 6) decisions about hormone treatment at diagnosis dependent on patient characteristics, mainly age and Gleason grade. In this paper, these studies are reviewed briefly and data are presented to support these conclusions. Some tentative treatment recommendations are proposed.—NCI Monogr 7:165-170, 1988.

The VACURG was organized in 1959 to investigate treatment of prostate and bladder cancer in randomized clinical trials. Over the next 15 years, approximately 4,000 patients with newly diagnosed prostate cancer were randomized to 1 of the 3 consecutive VACURG protocols (1-3). These studies came to an end in 1975 when a review committee of the National Cancer Institute disapproved a grant request for further studies, presumably believing that the era of endocrine treatment for prostate cancer was over and that further progress in treatment by endocrine manipulations seemed unlikely.

Recent studies with the luteinizing hormone-releasing hormone agonists have reawakened interest in the VACURG studies because they were large, well-conducted, randomized clinical trials and because a careful review of these studies might provide answers to questions needed for designing new protocols such as: 1) Has endocrine therapy been shown to increase overall survival? 2) If DES is used, what dose schedule should be studied? 3) Is it still permissible to have an untreated control group? These questions should be kept in mind as we review the 3 major VACURG studies.

In all VACURG studies, the patients were newly diagnosed, and the following staging system was used (fig.

1); stage I, incidentally found microscopic cancer; stage II, palpable cancer by rectal examination not extended beyond the prostatic capsule; stage III, local extension beyond the prostatic capsule; and stage IV, elevated prostatic acid phosphatase (determined by central laboratory) or demonstrated metastases. No patients had staging laparotomies and bone scans were not used in staging. Note that unlike many other staging systems, the VACURG put all patients with elevated acid phosphatase levels into stage IV. The data presented in table 1 provide justification for the use of acid phosphatase in staging prostate cancer patients. Note that the death rates from cancer were about the same for patients who only had elevated phosphatase levels and those who only had metastases. Both death rates were distinctly higher than that for stage III patients. These data strongly suggest that elevated acid phosphatase levels represent nondetectable distant metastasis.

This Consensus Development Conference is concerned with the management of clinically localized prostate cancer. According to the VACURG staging system, this would refer at most to stages I, II, and III as just presented. However, it is well-known today that many patients with these apparently clinically localized tumors actually have metastases in the regional lymph nodes. Because endocrine therapy is a systemic rather than a regional or localized form of treatment, we will not limit our discussion of the VACURG studies to patients in these 3 stages but rather present the data from all stages that we believe are pertinent to understanding the action, toxicity, and role of endocrine treatment in the management of patients with prostate cancer.

Study 1 was undertaken by the VACURG to find out how 5.0 mg DES daily compared with orchiectomy and to determine whether the 2 treatments together were better than either one alone (4). Accordingly, from 1960 until 1967, patients with stages III and IV prostate cancer were randomized into 4 treatment groups: placebo, 5.0 mg DES daily by mouth, orchiectomy plus placebo, and orchiectomy plus 5.0 mg DES. By the end of the study, about 475 patients were in each of the 4 groups. An additional 120 patients with stage I disease and 179 with stage II disease were randomized to either prostatectomy plus placebo or prostatectomy plus 5.0 mg DES daily by mouth.

The principal result of study 1 was that the 5.0-mg dose of DES was associated with an increased risk of death from cardiovascular causes (5). This effect is illustrated in figure 2, in which cumulative deaths from heart or vascular disease are plotted versus time for the 4 treatment groups of patients with stages III and IV disease. The excess cardiovascular toxicity of estrogen appears within the first year. A similar plot was observed for deaths from pul-

ABBREVIATIONS: VACURG = Veterans Administration Cooperative Urological Research Group; DES = diethylstilbestrol.

¹ Mention of trade names does not imply endorsement of the products by the United States Government.

² Biometry Branch, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, MD.

* Reprint requests to: David P. Byar, M.D., Biometry Branch, Division of Cancer Prevention and Control, National Cancer Institute, Executive Plaza North, Rm. 344, National Institutes of Health, Bethesda, MD 20892.





STAGE	RECTAL EXAMINATION	PROSTATIC ACID PHOSPHATASE	EVIDENCE OF METASTASES X-RAY OR BIOPSY
I	No Induration 	≤ 1.0 K.A.U.	0
II	Localized Nodule 	≤ 1.0 K.A.U.	0
III	Extra Prostatic Extension 	≤ 1.0 K.A.U.	0
IV	Any Findings 	> 1.0 K.A.U.	OR +

FIGURE 1.—Staging system used in all VACURG studies; KAU = tartrate-inhibitable portion of the serum acid phosphatase measured in King-Armstrong units.

monary emboli. This result surprised both the investigators and the general medical public and was not believed for some time by many. This effect was also seen (fig. 3) in stage I DES-treated patients who had a distinctly worse overall survival ($P < .05$). The cardiovascular hazard of 5 mg DES daily was not seen in patients with stage II disease. A possible explanation for this may be that stage I patients were usually diagnosed following transurethral resection, whereas stage II patients were diagnosed because of abnormal findings on rectal examination. Because all patients in stages I and II were to be treated by radical prostatectomy, most stage I patients had two major operations, the transurethral resection followed by the radical prostatectomy in a relatively short period, whereas this was not true for the stage II patients whose initial operation was usually only a needle biopsy of the prostate. In fact, we found that almost all the excess deaths that occurred among patients in stage I during the first year were confined to that group who had two operations within 2 months.

Analyses of time to progression for stage III patients (defined as time until first metastases or first increase in acid phosphatase or death from prostate carcinoma) showed that the 3 endocrine treatment arms had distinctly less rapid progression than did the placebo arm (fig. 4), but curves for overall survival showed no clear survival advantage for initial endocrine therapy in either stage III or stage IV, partly because of the excess cardiovascular deaths in the DES-treated arms. Orchiectomy plus 5.0 mg DES was no better than either treatment alone with respect to overall survival, but DES was more effective than orchiectomy

in preventing cancer deaths (6). When interpreting these results, it is important for one to note that in all VACURG studies the physician could change the patient's treatment if indicated because of symptoms or advancing disease. In fact, 44% of patients in stages III and IV assigned to placebo had their treatments changed later, and thus comparisons with the placebo group may more properly be interpreted as evaluations of immediate endocrine treatment at diagnosis versus delayed endocrine treatment, if a change was later required.

After the completion of study 1, 506 patients in stages III and IV were randomized to the second VACURG study in which placebo, 0.2 mg, 1.0 mg, and 5.0 mg DES, all daily and by mouth, were compared. This study was stopped early because once again a pattern of excess cardiovascular deaths in the 5.0-mg DES arm was beginning to emerge. This pattern was particularly prominent in stage III patients who were at less risk from cancer death than were stage IV patients (fig. 5). The principal finding of this study was that 1.0 mg DES had the same beneficial effects in retarding cancer progression as did 5.0 mg DES (fig. 6). The equivalence of the 1.0- and 5.0-mg doses of DES was also seen in plots of cause-specific survival for stage IV patients when cancer deaths only were used.

TABLE 1.—Study 3: death rates for patients in stage III and various categories of stage IV

Category	No. of patients	Deaths/1,000 patient-months		
		All causes	Prostate cancer	Cardiovascular disease
Stage III patients	531	11.8	2.1	5.1
Stage IV patients				
Increased acid phosphatase only	289	19.7	8.8	5.0
Metastases only	25	19.5	9.0	4.5
Both metastases and increased acid phosphatase	150	32.7	21.5	5.6

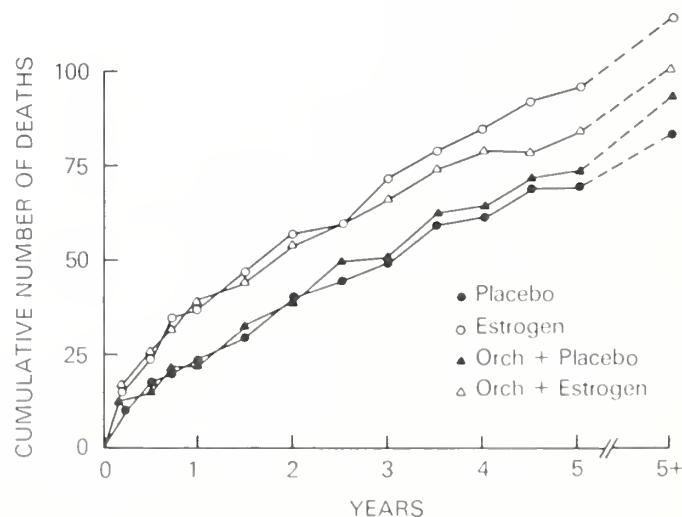


FIGURE 2.—Cumulative No. of deaths from heart or vascular disease for stage III and IV patients in study 1. Orch = orchiectomy.

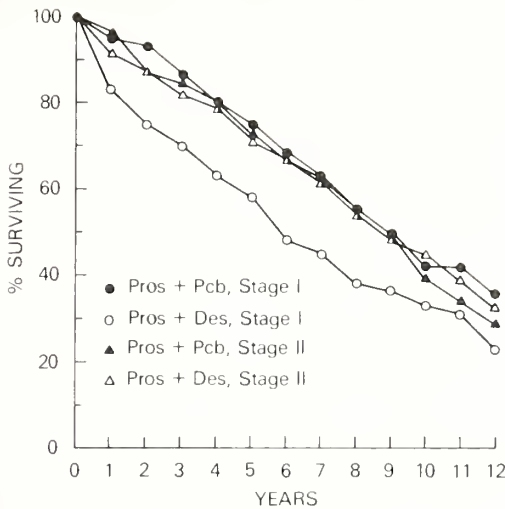


FIGURE 3.—Actuarial survival curves for all causes of death for patients in stages I and II in study 1. Pros + Pcb = prostatectomy and placebo.

Study 2 also showed that treatment with 1.0 mg DES beginning at diagnosis increased overall survival in stages III and IV patients compared with placebo (fig. 7). In addition, an analysis of study 2 data with a mathematical model incorporating covariate information (7) suggested that placebo or no treatment would be preferable for older patients with low-grade tumors, but immediate estrogen therapy might increase survival for younger patients with high-grade tumors.

Study 3 was begun in 1969. Patients with stage III or IV disease were randomized to 1 of 4 oral treatments given daily: 2.5 mg Premarin, 30 mg Provera, 30 mg Provera plus 1.0 mg DES, and 1.0 mg DES alone. Altogether, 1,112 patients were entered before the study was closed in 1975. Although there were no significant differences in overall survival between treatments, 1.0 mg DES was somewhat more effective than 2.5 mg Premarin or 30 mg Provera in retarding progression from stage III to IV, so that the overall

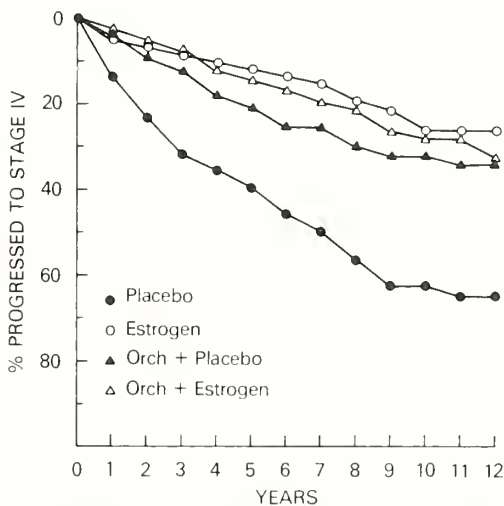


FIGURE 4.—Actuarial curves for progression from stage III to IV for patients in study 1. Orch = orchiectomy.

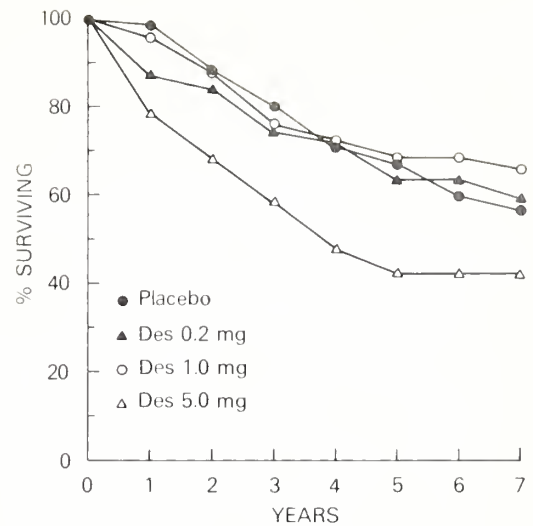


FIGURE 5.—Actuarial survival curves for deaths due to cardiovascular disease only for patients in stage III in study 2.

conclusion was that the other 3 endocrine treatment arms (at the doses studied) were not superior to 1.0 mg DES. Patients in study 3 were older than patients in studies 1 or 2. Results of exploratory data analysis suggested that the moderate benefit observed in the 2 treatment groups receiving 1.0 mg DES was most apparent in younger patients (<75 yr) with high-grade tumors (Gleason sum 7-10) and that there could be increased hazard of cardiovascular death for these 2 treatment groups compared with those receiving either Premarin or Provera alone for patients aged 75 or older.

From 1967 to 1975, patients with stage I or II disease were randomized to placebo or prostatectomy plus placebo. No significant benefit for radical prostatectomy was demonstrated (8). However, this result must be interpreted with caution because the study was small and modern staging methods were not used (9).

In conjunction with study 3, another clinical trial design-

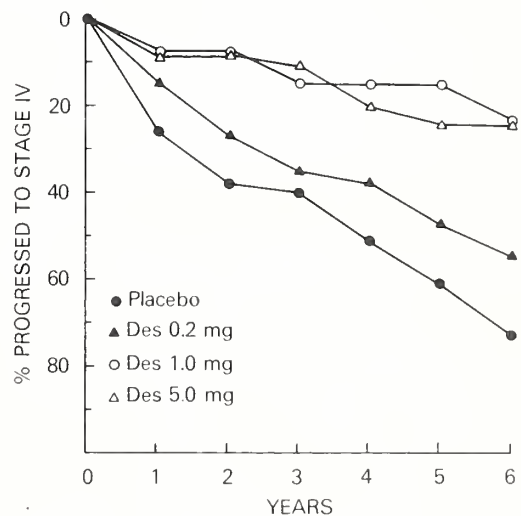


FIGURE 6.—Actuarial curves for progression from stage III to IV for patients in study 2.

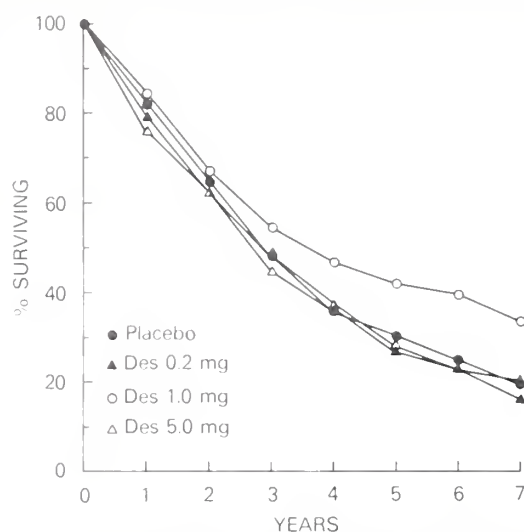


FIGURE 7.—Actuarial survival curves for all causes of death for patients in stages III and IV in study 2.

nated "Study 3, Phase II" was conducted for stage I and II patients who were either too old, too ill, or unwilling to be randomized to the trial just described in which radical prostatectomy was 1 treatment option. In this study, about 100 stage I and about 50 stage II patients were randomized to each of 2 treatments given daily by mouth, i.e., placebo or 1.0 mg DES. The results were puzzling because the estrogen treatment was found to be distinctly harmful in stage I patients (especially producing excess cardiovascular deaths), but estrogen treatment appeared to be protective in stage II patients. Summary data for this study are given in table 2. The 5-year survival rate for all causes of death in stage I was 61% for placebo- versus only 45% for DES-treated patients ($P = .026$). The corresponding rates in stage II, however, were 48% for placebo and 75% for DES ($P = .058$). The results were even more striking for survival curves constructed for cardiovascular causes only. The same reversal was noted with $P < .002$ favoring placebo in stage I but $P < .019$ favoring 1.0 mg DES in stage II. A recently proposed test for such cross-over or qualitative interactions (10) was significant at $P < .05$ for all causes of death and $P < .025$ for cardiovascular deaths. Despite this evidence for a statistically significant interaction, our overall impression is that the results in stage II are anomalous because the pattern of causes of death shown in table 2 seems implausible in light

of the results from the 3 main studies. What this study does suggest is that even 1.0 mg DES can be associated with increased hazard of cardiovascular death in older patients.

DISCUSSION AND CONCLUSIONS

We have tried to review briefly the highlights of about 15 years of research on over 4,000 patients, with emphasis on what can be said about hormonal treatment of prostate cancer. Other important findings from this series of studies, such as the development of the Gleason grading system, the general importance and refinement of knowledge about prognostic factors (11), and changes in laboratory values associated with treatment for prostate cancer, have been described elsewhere (2). Concerning hormonal treatment, six main conclusions can be derived from the VACURG studies.

Cardiovascular Hazard of 5.0 mg Diethylstilbestrol

This is probably the finding for which the VACURG studies are best known. It is almost certain that this finding would never have emerged if a large randomized clinical trial had not been conducted because it is commonplace for older men such as those who get prostate cancer to die of cardiovascular causes. For several decades, such deaths were regarded as triumphs of treatment because the patients were not dying of prostate cancer! For several years after the first publication of this finding, many physicians did not believe it, but now it appears to be accepted generally.

Orchiectomy Plus Diethylstilbestrol No Better Than Orchiectomy or Diethylstilbestrol Alone

The VACURG studies were originally set up to determine whether orchiectomy plus estrogen was better than either used alone. In a large observational study published in 1950, Nesbit and Baum (12) suggested that the combination was superior. Our conclusion that they are equivalent refers to survival from all causes of death. However, data from study 1 suggest that 5.0 mg DES daily are somewhat more effective than orchiectomy alone in retarding the growth of the cancer. This is seen both in plots of time to progression for stage III patients (fig. 4) and in survival curves constructed for cancer deaths only (not shown).

Equivalent Effect of 1.0 and 5.0 mg Diethylstilbestrol on Cancer

The data from study 2 clearly showed that the 1.0-mg dose of DES was equivalent in its effect on the cancer to

TABLE 2.—Summary results for study 3, phase II

Stage	No. of patients	No. of deaths			Five-yr survival, %	No. who progressed	Progression rate ^a
		Prostate cancer	Cardiovascular	Other (unknown)			
Stage I							
Placebo	98	1	10	17 (3)	61	5	1.34
1 mg DES	107	4	29	12 (1)	45	7	2.06
Stage II							
Placebo	45	3	16	3 (0)	48	11	7.41
1 mg DES	48	4	7	3 (1)	75	7	3.58

^a Progression rate is expressed as the number of patients progressing/1,000 patient-months of observation.

that of the 5.0-mg dose. However, it is known that 1.0 mg DES daily is not sufficient to suppress serum testosterone to castrate levels (13,14). Because of this, many urologists currently use 3.0 mg DES (1.0 mg three times a day) in treating prostate cancer. We suspect strongly that this dose is too large. To our knowledge, 1.0 and 3.0 mg DES have never been compared in a randomized trial. We think it is more important to treat the prostate cancer than to treat the serum testosterone. Nevertheless, one must wonder how a dose of estrogen insufficient to suppress completely the serum testosterone could be as effective as the larger dose, which does suppress testosterone to castrate level. We suggest that the equivalence of the 1.0- and 5.0-mg doses plus the apparent superiority of 5.0 mg DES over orchiectomy alone in retarding cancer growth indicate that DES acts directly on the cancer cells in addition to inhibiting testosterone secretion. In an electron microscopic radiographic study, Sinha et al. (15) detected in vitro nuclear binding of radiolabeled estradiol in prostate cancer cells.

Reduced Cardiovascular Hazard for 1.0 mg Diethylstilbestrol

The data from study 2 clearly showed that 1.0 mg DES had a lower cardiovascular hazard than did the 5.0-mg dose and, in fact, that hazard did not appear to be elevated compared with that for the group initially treated with placebo. However, as we have noted, study 2 was stopped early because again the cardiovascular toxicity of estrogen was detected; therefore, it is a smaller study than either study 1 or 3. For this reason, conclusions are less certain. The data from study 3 described in this article, both the main study and the special study (phase II) for stages I and II patients, suggest that even a daily 1.0-mg dose of DES is associated with increased hazard of cardiovascular death in susceptible patients, particularly older men.

Premarin or Provera No Better Than 1.0 mg Diethylstilbestrol at Doses Studied

Study 3 was a large study, yet we were unable to demonstrate that either Premarin or Provera was superior to 1.0 mg DES in its effect on overall survival in either stage III or stage IV patients. These results clearly depend on the doses chosen for these other agents, but we are unaware of any randomized clinical trials demonstrating that any endocrine treatment is superior to 1.0 mg DES in its effect on the prostate cancer. The possibility of cardiovascular side effects cannot be ignored, and in making a choice of therapy, a physician should take both efficacy and toxicity into account.

Decisions About Hormone Treatment at Diagnosis Dependent on Patient Characteristics

Whether endocrine treatment for patients with prostate cancer should begin at diagnosis remains an important question. The results presented in figure 7 suggest that patients in stages III and IV begun on treatment with 1.0 mg DES by mouth at diagnosis survive longer than patients begun on placebo, but the difference in overall survival is unimpressive for the first 3 years. We are tempted to say nothing further because these are the results of a properly conducted randomized clinical trial. However, in 2 papers

(7,16), we applied sophisticated mathematical models to determine which patients were most likely to benefit from treatment, and recently an independent analysis suggested results similar to ours (17).

We admit that conclusions based on such exploratory data analyses are not as firm as those based on randomized comparisons. However, we believe that such analyses may help clinicians interpret randomized clinical trial results and suggest hypotheses to be examined in future studies. Accordingly, it is our overall impression that the question of whether to treat newly diagnosed patients with prostate cancer depends on the characteristics of the patients. In our analyses, the most important factors for choosing whether to treat at diagnosis were the patient's age and the histologic grade of his tumor. In the simplest terms, we believe that younger patients with high-grade tumors are the most likely to benefit from the therapy with DES, whereas older patients with lower grade tumors may actually be harmed. These results may well not apply to other forms of endocrine therapy.

RECOMMENDATIONS

Based on these six main conclusions and our understanding of them as just presented, we tentatively put forth some treatment recommendations that might be considered appropriate either for treatment of individual patients or in the design of future randomized clinical trials. Even with the data from randomized clinical trials, treatment recommendations are difficult because the question of the generalizability of the results almost always requires speculation beyond what was actually observed. We wish to distinguish clearly these tentative treatment recommendations from the conclusions we have just presented. However, we believe strongly in the first treatment recommendation. In summary, our tentative recommendations are the following:

- 1) If DES is used, the initial dose should not exceed 1.0 mg daily.
- 2) Patients in stages I-III with low-grade tumors (Gleason score 2-6) probably do not need hormone therapy.
- 3) Patients with higher grade tumors (Gleason score 7-10) may benefit from hormone therapy begun at diagnosis.
- 4) Endocrine therapy other than DES should probably be considered for patients over age 75.

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Hormonal Therapy for Locally Advanced Prostate Cancer

Albert B. Einstein, Jr.¹

ABSTRACT—A patient with locally advanced prostate cancer (stages C and D1) has a poor prognosis with a high risk of developing and dying of distant metastases. Hormonal therapy is the major form of systemic therapy for metastatic (stage D2) prostate cancer. The most commonly used forms of hormonal therapy are orchiectomy, diethylstilbestrol, and luteinizing hormone releasing hormone, agonists that prevent the stimulation of tumor cells by testosterone. They produce a 60%–80% symptomatic or objective response rate, but their ability to prolong overall survival remains uncertain. Surgical adrenalectomy, hypophysectomy, and pharmacologic adrenal suppression prevent the clinically less significant adrenal androgen stimulation of tumor cells. Antiandrogens competitively inhibit the interaction between androgens and cytosolic androgen receptors. Complete androgen blockade (luteinizing hormone releasing hormone agonist and antiandrogen) was initially espoused to be superior to single-agent hormonal therapy, but preliminary results from a multigroup randomized trial suggest that it has only a minimal advantage. The benefit of hormonal therapy in stages C and D1 prostate cancer at the time of diagnosis has not been clearly established. Available studies are few, and most often they are uncontrolled or include only small numbers of patients. However, they suggest that the early use of hormonal therapy prolongs disease-free survival but does not prevent ultimate disease progression or prolong overall survival. Hormone receptor assays may be helpful in the selection of patients who would benefit from early hormonal therapy.—NCI Monogr 7:171–174, 1988.

Locally advanced prostate cancer is a systemic disease. Poor prognosis correlates with advanced clinical stage (large size of tumor, extracapsular extension, and regional node metastases), poor tumor differentiation, and elevation of serum acid phosphatase (1). Patients with clinical stage C and surgical stage D1 disease have a high risk of occult distant metastases which, if the patient lives long enough, will become clinically apparent and lead to death (2). Improvement in the survival of patients with these stages of disease requires effective adjuvant systemic therapy in combination with effective local therapy that will either delay or prevent the appearance of the distant metastases.

In 1941, Huggins and Hodges (3) first demonstrated that prostate cancer growth was dependent on androgenic stimulation. In addition, they reported that orchiectomy or pharmacologic doses of estrogens clinically benefited patients with metastatic prostate cancer. Subsequently, hormonal therapy designed to interfere with androgen stimulation

has been the standard form of systemic therapy for prostate cancer.

Despite the early development of hormonal therapy, continued controversy surrounds several basic issues:

- 1) the effect of hormonal therapy on the overall survival of patients with metastatic disease;
- 2) the relative effectiveness of the different forms of hormonal therapy; and
- 3) the benefit of early application of hormonal therapy in stages C and D disease compared with utilization of this therapy to the patient who is symptomatic due to progressive disease.

ANDROGEN HORMONE PHYSIOLOGY

Testosterone, produced by the testis and the principal androgen that stimulates normal prostate and prostate cancer cell growth, constitutes 95% of the androgen circulating in the serum (4). Androstenedione and dehydro-3-epiandrosterone, both produced by the adrenal glands, compose the other 5%. Ninety-five percent of the serum testosterone is protein-bound to sex hormone-binding globulin with less affinity for serum albumin. Only free serum testosterone is capable of entering the prostate cell to influence its metabolism. It passes through the cell membrane passively and is converted enzymatically to DHT, which combines with a cytoplasmic androgen receptor. This complex enters the nucleus and interacts with the genetic material to cause an increase in messenger RNA synthesis and subsequently protein synthesis (fig. 1).

Testosterone production is regulated by the hypothalamic pituitary gonadal feedback mechanism (fig. 2). The hypothalamus of the brain produces LH-RH, which stimulates the pituitary gland to secrete LH. The LH stimulates the Leydig cells of the testis to produce testosterone, which then reacts with hypothalamic receptors to prevent further release of LH-RH. In a similar feedback mechanism, the synthesis of adrenal androgens is controlled by the production of adrenocorticotrophic hormone by the pituitary gland, which stimulates the adrenal gland to produce cortisol and androgen (fig. 2). Cortisol interacts with the hypothalamus to inhibit further production of adrenocorticotrophic hormone releasing hormone.

HORMONAL THERAPY FOR PROSTATE CANCER

The objective of physicians in prescribing hormonal therapy for prostate cancer is to reduce the production of androgens or block the effect of the androgens on the cancer cell. The different types of hormonal therapy have been developed with physicians' increasing knowledge of the physiology of androgen synthesis and regulation and the effect of androgen on the cancer cell.

ABBREVIATIONS: DHT = dihydrotestosterone; LH-RH = luteinizing hormone releasing hormone; DES = diethylstilbestrol; VACURG = Veterans Administration Cooperative Urological Research Group.

¹ Division of Hematology and Medical Oncology, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98111.

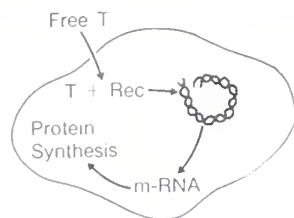


FIGURE 1.—Testosterone (T) stimulation of prostate cancer cells via receptor (Rec) interaction.

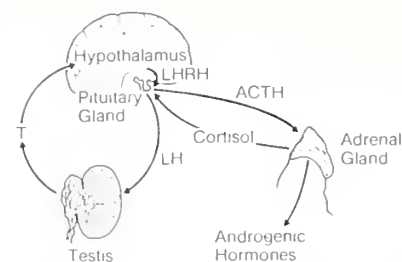


FIGURE 2.—Hypothalamic pituitary regulation of testosterone (T) and adrenal androgen hormone synthesis.

Bilateral orchiectomy is the hormonal treatment with which all others must be compared. It removes the source of testosterone, which accounts for 95% of the circulating androgens (4). The procedure is simple and results in rapid symptomatic response. The major disadvantages of the treatment are the psychologic trauma associated with castration and the loss of potency (5). Palliative effects of orchiectomy are observed in 60%–80% of the patients and include subjective pain relief and objective reduction in primary tumor size, soft tissue metastases, and ureteral dilation. The duration of the palliative response is limited to 12–18 months. Despite objective and subjective responses, the impact of orchiectomy on overall survival has been uncertain. Reported studies included nonrandomized or historical untreated control groups (6), or randomized placebo or control groups; patients ultimately received hormonal therapy when their disease progressed (7).

The synthetic compound DES directly inhibits the hypothalamic production of LH-RH and indirectly LH and testosterone (4). The VACURG studies have demonstrated that 1- to 3-mg daily doses of DES produce palliative responses similar to orchiectomy (7). Possible side effects include gynecomastia, loss of libido, and loss of potency. However, a 5-mg daily dose is associated with an increased death rate due to cardiovascular complications, such as myocardial infarction, congestive heart failure, and thromboembolic complications, which offset any therapeutic advantage. The combination of orchiectomy and DES does not enhance the response rate. Patients who fail to respond to either orchiectomy or DES or progress after initial response to either treatment rarely respond to the alternative treatment.

The definition of the amino acid sequence of the decapeptide LH-RH and the subsequent synthesis of analogs with greater potency have provided an alternative method to suppressing testosterone production. Synthetic LH-RH agonists, such as leuprolide or Buserelin (Farbwerke Hoechst AG, Frankfurt, Federal Republic of Germany), initially stimulate the pituitary gland to produce increased levels of LH and subsequently testosterone during the first 2 to 4 weeks of administration. Continued treatment subsequently causes a decrease in LH production and a decline in production to orchiectomy levels (8). The Leuprolide Study Group (9) has compared leuprolide and DES in patients with stage D disease. They (9) reported an 86% response rate for leuprolide compared with 85% for DES and a 1-year survival rate of 87% compared with 78%, respectively. The LH-RH agonists are relatively nontoxic but can cause an

increase in symptoms such as bone pain during the first 2 to 4 weeks due to the increased testosterone production. In addition, the initial forms of this drug required daily parenteral injections or intranasal administration. A new depot form is now available that is administered monthly.

Second-line hormonal therapy following progression after orchiectomy or DES had been directed toward the suppression of adrenal androgen production by surgical adrenalectomy (10), hypophysectomy (10), or medical suppression of adrenal function with prednisone or aminoglutethimide (11). Unfortunately, they result only in brief subjective responses in 20% to 40% of the patients. This result suggests that the role of adrenal androgens in stimulating prostate cancer growth is minimal.

Antiandrogens (flutamide, cyproterone acetate) are chemicals that compete with DHT for the cytoplasmic androgen receptor (12). The antiandrogen-receptor complex is inactive. These agents have clinical activity similar to DES with less toxicity. Control trials during which antiandrogens were compared with DES or orchiectomy have not been completed; therefore, response rates have not been carefully defined. The use of antiandrogens as a single agent is limited by a secondary increase in gonadotropin hormone and androgen production due to the neutralization of the inhibitory feedback action of androgens at the hypothalamic level. Progressively higher doses of antiandrogens are required to neutralize the rising level of testosterone.

Complete androgen blockade has been advocated by Labrie et al. (13) to be the optimal hormonal therapy because it eliminates the effect of both testicular and adrenal androgens. Labrie and his associates treated 47 patients with stage D prostate cancer with leuprolide to suppress the production of testosterone and with flutamide to block the effect of adrenal androgens. They reported a 100% positive response rate and only a 3.3% death rate after 1½ years of follow-up. The combination hormonal therapy also produced a positive response in 36% of stage D patients previously treated with DES. Labrie believes that untreated prostate cancer is exquisitely sensitive to androgens and that the adrenal androgens do play a significant role in stimulating progression of disease in patients treated only with orchiectomy or DES. Moreover, he believes that androgen-insensitive clones arise only when androgen blockade has been incomplete.

Stimulated by these results, an intergroup study was initiated in the United States in which 617 patients with stage D prostate cancer were randomized to receive either leuprolide plus flutamide or leuprolide alone (14). Preliminary re-

sults after a 20-month follow-up indicate only a minimally significant difference in time to progression of disease in favor of the combined therapy. Thus it appears that the addition of flutamide to an LH-RH agonist might offer some slightly increased advantage, but not to the degree originally proposed by Labrie.

EARLY USE OF HORMONAL THERAPY FOR LOCALLY ADVANCED DISEASE

Controversy continues regarding whether hormonal therapy is best used early in asymptomatic patients with locally advanced prostate cancer or whether it should be reserved for the time when the patient develops symptomatic metastases. Unfortunately, good randomized controlled trials that address this specific question do not exist.

In 1950, Nesbit and Baum (6) reported that patients with various stages of prostate cancer treated with hormone therapy had a 5-year survival of 20% compared with 9% for a historical control group that was followed before it was generally known that prostate cancer was a hormonally sensitive tumor. This information has been extrapolated to mean that patients would best be treated by hormonal therapy at the time of diagnosis for both locally advanced and metastatic disease whether or not they are symptomatic. This study obviously suffers from the difficulties of comparisons of treatment results with a historical control group.

In the first VACURG study, patients with various stages of prostate cancer were treated with placebo, DES, orchiectomy and placebo, or orchiectomy and DES. The daily dose of DES was 5 mg (15). Of the patients with stage C disease, the total deaths were similar in all 4 groups, which suggests that hormonal therapy did not prolong survival compared with the placebo group. However, further analysis indicated that many of the patients initially in the placebo group were treated with hormone therapy at a later date when their disease progressed. Therefore, the control group was not truly untreated. With this in mind, the data suggest that early hormonal therapy does not improve overall survival compared with delayed treatment. Patients treated with DES experienced fewer cancer-related deaths but a greater number of cardiovascular-related deaths than the placebo patients, a finding that offsets the advantage of the treatment.

In the second VACURG study, patients were treated with either placebo, 0.2 or 1 mg, or 5 mg DES (16). Patients with stage C disease had a decreased cancer-related death rate if they received 1 mg or 5 mg DES compared with placebo or 0.2 mg DES. Again, the high death rate due to cardiovascular problems was noted with the 5-mg but not with the 1-mg dose. In addition, 1 mg and 5 mg DES were reported to delay the progression of disease from stage C to stage D. The VACURG studies suggest that hormonal therapy delays progression of disease from early to advanced stage, but it does not prolong overall survival.

Taylor and his colleagues (17), reporting on 221 patients with clinical stage C disease treated primarily by definitive external radiotherapy, found no difference in overall survival between those patients treated with or without DES. The 5-year survival rate for both groups was 57%.

Zincke and Utz (18) have reported results of patients with stage D1 disease treated with radical prostatectomy and lymph node dissection, many of whom also had or-

chiectomies. In this nonrandomized study, castrated patients had a 5-year nonprogression rate of 95% compared with 18.5% for patients not treated with orchiectomy. The castrated patients also had higher (though not significant) survival rates of 94% at 5 years and 85% at 10 years. In all treatment groups, the number of positive nodes adversely affected progression and survival. This experience suggests that early hormonal treatment is beneficial for locally advanced disease following extensive surgery. Unfortunately, the study is nonrandomized and contains a relatively small number of patients.

TUMOR CELL HETEROGENEITY

Tumors that respond to hormonal therapy contain a significant number of androgen-sensitive cells. Progression of disease after hormonal therapy results from the emergence of androgen-resistant cell clones, which may arise due to clonal selection or cell adaptation (19). If clonal selection is primarily operative, mutations causing androgen-resistant cells are more likely to occur the longer the tumor grows. These clones may arise before diagnosis and treatment are established or later, after treatment has been started. The early use of hormonal therapy before resistant cells are prevalent could be theoretically justified, particularly if androgen sensitivity could be predicted by simple convenient tests.

ANDROGEN SENSITIVITY ASSAYS

The ability of physicians to identify patients with androgen-sensitive tumors at high risk of occult distant metastases might lead to more rational early treatment. Gleason histologic grade of tumor, intracellular DHT levels, cytosol androgen receptor content, and nuclear androgen receptor content have been studied for their ability to predict hormone responsiveness (20-22). Trachtenburg and Walsh (20) reported a correlation between nuclear androgen receptor content and duration of subjective and objective responses to hormone therapy. A significantly increased disease-free interval was observed in patients treated with hormonal therapy with DHT levels greater than 2 ng/g in prostate tissue compared with patients with values less than this (21). Benson and his colleagues (22) have recently found that the time to progression following hormonal therapy correlated with the nuclear and total androgen receptor binding, but not with cytosol androgen receptor binding. In addition, histologic grade 4 lesions were the least responsive to hormonal therapy. Unfortunately, these assays are not practical enough at this time for general applicability. With more practical useful assays, patients with locally advanced disease might be selected for further studies in which the potential benefit of hormone therapy in the adjuvant setting would be evaluated.

CONCLUSIONS

The early use of traditional suppressing hormone therapy for clinical stages C and D0 and pathologic stage D1 disease may prolong disease-free survival, but there is no conclusive evidence that it prevents disease progression or prolongs overall survival. Unfortunately, the few studies in which investigators attempted to evaluate effect on disease-

free survival have been poorly designed. Prolongation of disease- and symptom-free survival for this elderly male population may be of considerable benefit and thus a goal worthy of achievement.

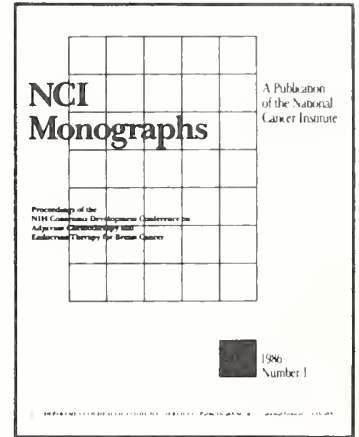
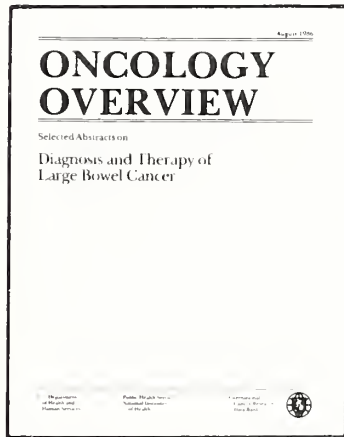
Areas of future research in the early use of hormonal therapy in patients with locally advanced disease that physicians might consider include the:

- 1) effect of complete androgen blockage by the combination of orchiectomy or an LH-RH agonist plus an antiandrogen on the rate of progression of disease and overall long-term survival;
- 2) degree of heterogeneity of early tumors regarding androgen sensitivity and insensitivity and identification of factors that influence the development of insensitivity;
- 3) correlation of predictors of hormone-sensitive tumors with clinical results of adjuvant hormonal trials;
- 4) benefit of adjuvant combination hormonal therapy, chemotherapy, and/or immunotherapy in delaying progression and prolonging survival, with the assumption of future development of effective agents;
- 5) development of new agents that take advantage of the hormonal responsiveness of prostate cancer; and
- 6) potential value of androgenic stimulation of prostate cancer to enhance its susceptibilities to cycle-specific cytotoxic therapy.

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Number 8

Smokeless Tobacco Use in the United States

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Smokeless Tobacco Use in the United States

A Compilation of Papers on Recent Research

and Discussion of Directions for

Future Research

Smoking, Tobacco, and Cancer Program
Division of Cancer Prevention and Control
National Cancer Institute
Bethesda, Maryland

Scientific Editors:
Gayle M. Boyd
Charles A. Darby

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Foreword

In 1986, the Public Health Service completed the first comprehensive, in-depth review of the relationship between smokeless tobacco use and health, *The Health Consequences of Using Smokeless Tobacco: A Report to the Surgeon General*. It identified three major health risks associated with the use of smokeless tobacco: oral cancer, the development of leukoplakias and other oral conditions, and nicotine addiction. In the intervening years, these findings have been confirmed and strengthened by continued research.

The 1986 Report described an alarming pattern of increasing prevalence of smokeless tobacco use in the United States, especially among youth, and data presented in this monograph indicate little change in that pattern. Smokeless tobacco use has a long history in this country but declined markedly during the first half of this century due, in part, to health concerns about spitting. The reemergence of snuff and chewing tobacco use when the attendant health hazards are so well documented is unacceptable.

Over 350,000 lives are prematurely lost each year due to cigarette smoking. It is imperative that smokeless tobacco not be allowed to add to this unnecessary toll. Cigarette smoking has declined over the past twenty years, due in great measure to the combined efforts of biomedical scientists, public health experts, and organizations in the private sector, particularly the American Cancer Society, the American Lung Association, and the American Heart Association. It is important that a comparable effort now be directed toward reducing the use of smokeless tobacco. Indeed, the public must be made aware that **there is no safe form of tobacco use.**

The papers in this monograph present the most current national survey data on smokeless tobacco prevalence and explore the nature of tobacco use by youth. These papers represent a valuable contribution to our understanding of smokeless tobacco practices by youth; they will be invaluable in the development of effective interventions. Intervention efforts are urgently needed to educate the public regarding the hazards of using **any** form of tobacco, to prevent youth from initiating tobacco use, and to encourage and assist attempts at quitting. I congratulate the National Cancer Institute and other health agencies for their efforts, and I strongly encourage those interested to make the elimination of tobacco use in all its forms a number one priority for health promotion and disease prevention.



C. Everett Koop, M.D.
Surgeon General

Preface

The National Cancer Institute has set a goal of reducing cancer morbidity and mortality by 50% by the year 2000. As part of the Institute's strategy to attain that goal, the Smoking, Tobacco, and Cancer Program, within the Division of Cancer Prevention and Control, is funding a number of research trials to develop and evaluate interventions designed to prevent and reduce tobacco use among children and adolescents. Although many of the intervention programs focus primarily on cigarette smoking, valuable data are also collected on smokeless tobacco use.

The Smoking, Tobacco, and Cancer Program sponsors regular meetings each year to help investigators profit from each other's experience and scientific perspective. In addition, these interactions created the collaborative opportunity wherein the articles included in this monograph were developed. Additionally, several authors were especially invited to contribute papers that were considered critical to a full understanding of the current problem of smokeless tobacco use in the United States. These papers include a review of the cancer risk associated with smokeless tobacco, reports from recent national probability surveys regarding its use, and a summary discussion of future directions for research.

Some of the contributors to this monograph have received support from, or are affiliated with, the American Cancer Society; the National Heart, Lung, and Blood Institute; the National Institute on Drug Abuse; and the Centers for Disease Control, including the Office on Smoking and Health and the National Center for Health Statistics.

Joseph W. Cullen, Ph.D.

Gayle M. Boyd, Ph.D.

Smokeless Tobacco Use Among Adolescents: A Theoretical Overview

Mario A. Orlandi¹ and Gayle Boyd²

ABSTRACT—Prevalence data that are currently available indicate that smokeless tobacco use among youths in various parts of the United States is a significant and growing problem. Although relatively little is known about the factors that contribute to the initiation and maintenance of this behavior, previous research focusing on other substance use provides a valuable framework for both a study of smokeless tobacco use and the design of effective interventions for its prevention. The papers presented in this monograph address many of the gaps in our current knowledge and provide an accurate overview of research efforts in this area to date.—NCI Monogr 8:5-12, 1989.

During most of this century, the use of chewing tobacco and oral snuff, collectively referred to as SLT, was confined primarily to rural areas and particular occupational groups, such as miners and agricultural workers (1, 2), and prevalence was highest among persons over the age of 50 years (3). Recently, however, the numbers of reports from schools about SLT use by children and adolescents have been increasing. These observations have coincided with new biomedical and epidemiologic evidence implicating its use in the development of oral cancer.

In response to such reports and to a request from the Federal Trade Commission, the Surgeon General appointed a special Advisory Committee to review the available scientific literature on health risks associated with SLT. The report from the committee, "The Health Consequences of Using Smokeless Tobacco" (3), concluded that its use can cause cancer in humans and that this association is strongest for cancers of the oral cavity. Addressing noncancerous effects, the report concluded that SLT can cause oral leukoplakia and gingival recession and that its use can lead to nicotine dependence or addiction. The International Agency for Research on Cancer (4) and the National Institutes of Health Consensus Development Conference on Health Implications of Smokeless Tobacco Use (5) independently reached similar conclusions. Evidence relating to the cancer health risk associated with SLT use has been reviewed elsewhere (6) and is also summarized in this monograph by Mattson and Winn (7).

Because large-scale use of SLT by youths is such a recent phenomenon, relatively little is known about the pre-

dictors of onset, the factors influencing use, the patterns developed, and the relationship of its use to that of other substances. Such information is essential for the development of effective intervention strategies. This introduction to the studies that follow provides an overview of what is currently known regarding the nature and the magnitude of this growing public health problem.

PREVALENCE OF SMOKELESS TOBACCO USE

Description of Product

Of the two major forms of SLT, oral snuff and chewing tobacco (3, 8), snuff is finely ground or shredded tobacco to which various sweeteners and flavorings have been added. It is available in both dry and moist forms, but moist snuff is by far the more popular product. A user places a small amount or "pinch" in the mouth, and holds it in place between the lip and gum. Moist snuff is available in small sachets similar to tea bags or may be packaged loosely. Dry snuff is a fine powder and may be taken nasally as well as orally, although this practice is rare in the United States. Chewing tobacco is much coarser than snuff and is available in three forms: Loose leaf, by far the most popular, consists of small strips of shredded tobacco packaged loosely. Chewing tobacco may also be compressed into "plugs" or "bricks" or twisted into ropelike strands. All forms may be chewed or held in place in the mouth.

Both chewing tobacco and snuff are used orally and nicotine is absorbed through the oral mucosa. The resulting blood nicotine levels are comparable to those achieved by smokers, although the time courses differ. The SLT produces prolonged, sustained levels of nicotine in the blood that contrast to the rapid rise, peaks, and troughs that characterize cigarette smoking (9-12). The amount of nicotine absorbed is a function of the brand used, the amount of tobacco taken at one time, the length of time it is held in the mouth, and other individual variables.

National Surveys

Three recent surveys provide data on SLT use by adults. 1) In 1985, the Office on Smoking and Health sponsored a supplement to the CPS that included questions on SLT use. Due to sample structure and the large sample size of 114,000 individuals aged 16 years and over, estimates of the prevalence of its use can be calculated individually for states. These data are presented in this monograph by Marcus et al. (13). 2) In 1986, the same office included a number of questions on SLT in the Adult Use of Tobacco Survey. This telephone survey collected information from 13,031 persons aged 17 and older. Data are reported by

ABBREVIATIONS: SLT = smokeless tobacco; CPS = Current Population Survey; NHIS = National Health Interview Survey; NIDA = National Institute on Drug Abuse.

¹ Division of Health Promotion Research, American Health Foundation, 320 East 43rd St., New York, NY 10017.

² Smoking, Tobacco, and Cancer Program, Division of Cancer Prevention and Control, National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

Novotny et al. (14). 3) The Division of Cancer Prevention and Control of the National Cancer Institute in 1987 included questions on tobacco use in their Cancer Control Supplement to the NHIS, conducted by the National Center for Health Statistics. Preliminary data from the first quarter, representing 4,735 males aged 18 and over, have been reported elsewhere (15).

The NIDA included a question on SLT on the National Household Interview Survey conducted in 1985. This periodic household interview of persons aged 12 years and over provides the only national probability data currently available on SLT use by persons under 17 years of age. There are no national data on use by children under 12. Estimates from the NIDA survey indicate that 20% of males aged 12 through 17 used it sometime in 1985. A complete analysis of these data is presented by Rouse (16). Due to differences in question format, estimates from the NIDA survey cannot be compared directly with the other national surveys.

Estimates for prevalence of SLT use derived from the first 3 surveys are shown in table 1. Data from the 1970 NHIS are shown for comparison purposes. Variation among estimates from the 3 recent surveys may be attributed to differences in methodology. The 1985 CPS and the 1970 NHIS included approximately 45% proxy data, which are likely to result in underestimates, especially for snuff use. The 1986 Adult Use of Tobacco Survey did not use proxy data, but the relatively low response rate (74.3%) and the use of telephone interviews may have resulted in underestimates (17). Although the 1987 NHIS was a household interview survey without the use of proxy respondents, data represent the first quarter of 1987 only and the resulting estimates must be considered preliminary.

Given the above caveats, it is clear that use of SLT, especially snuff, has increased among the adult male population. Additionally, all the recent national surveys discussed in this monograph indicate that the highest rates of use occur among adolescent and young adult males (13-15, 17).

Regional and Local Studies

Regional and local prevalences are often much higher than national estimates (3). Bauman and co-workers (18) present data on all age groups from a large random sample

of 10 Standard Metropolitan Statistical Areas in southeastern United States. Because information on SLT use by youth was collected by adult proxy respondents, the resulting estimates are likely to underrepresent actual use by children. Despite this, it should be noted that there were reports of current use by children under the age of 4 years and that the estimates obtained for adult use were comparable to the 1985 CPS figures for this region of the country (13).

Considerable regional variation has been reported in the use of snuff and chewing tobacco by youth and adults. For example, use appears to be more common in rural areas, small communities, and in areas where regular use is traditional, although high rates have been reported in some metropolitan areas as well (3, 16, 19).³ Marcus et al. (13) found prevalence among adults highest in states with larger rural populations. The studies reported in this monograph cover geographic areas ranging from rural to suburban and metropolitan regions in the West, Northwest, North Central, Midwest, Southeast, and Northeast regions of the country. Prevalence estimates among adolescent males for "having ever used" SLT were consistently high, over 62% in most areas. Rates for more frequent use were lower and ranged from 11% to 18%.

Within all parts of the country, regular use is confined almost exclusively to males, although substantial numbers of females may experiment with SLT (3, 20, 21).³ Often, use by females is not reported because so few are involved. This trend toward increased use among adolescent males relative to females appears to be the reverse of that observed for cigarette smoking (22, 23). One marked exception to this pattern occurs among Native Americans, in whom substantial use of SLT tobacco by females has been observed [(19, 24, 25); Batliner T, Kaltenbach R, Bothwell E: Unpublished manuscript]. Native American males have higher rates than contemporary youths of other ethnic groups, although this pattern is not always observed (19) and may reflect the strength of traditional cultural practices. Batliner et al. (unpublished observations) observed differences in use between Native American youths living on and off reservations, and this was particularly marked among females. Schinke and associates (26) discuss its use among young Native Americans living on reservations in Washington State.

Generally, blacks and Asians are less likely to use SLT than are whites and Hispanics (19, 27).³ Similar trends have been observed in those studies reporting data by ethnic group (18), although in Los Angeles, the observed differences in use between black and white youths were less than in some other areas (28). National studies of adult use consistently find highest prevalence among whites and lowest among blacks (13-15, 17). Racial differences in use of SLT vary regionally, especially Hispanic prevalence relative to other groups (13). Data reported by Bauman et al. (18) on adults in the Southeast indicate that racial differences in use vary considerably across age groups.

Because no national data on use by adolescents prior to 1985 are available, researchers cannot track changes

TABLE 1.—Prevalence (%) of SLT use by males in the United States:
Four national surveys

SLT	NHIS, 1970 ^a	CPS, 1985 ^b	1986 ^c	NHIS, 1987 ^d
Snuff	1.4	1.9	2.4	3.2
Chewing tobacco	3.8	3.9	3.3	4.1
Any form	^e	5.5	5.2	6.2

^a Males were ≥ 17 yr old. Survey was by household interview with extensive use of proxy respondents (3).

^b Males were ≥ 16 yr old. Survey was by household interview with extensive use of proxy respondents (13).

^c Adult Use of Tobacco Survey (AUTS) was done of males ≥ 17 yr old by telephone survey (14).

^d Males were ≥ 18 yr old. Survey was done by household interview (15).

^e No information was available for this category.

³McCarthy D, Krakow M: Unpublished manuscript.

in consumption by youths nationwide. Anecdotal reports suggest a steady increase in prevalence over the past 10 years. Adult surveys indicate that over the past 15 years the increase in SLT use by young adults (under age 30) has been marked, whereas prevalence among older adults has either remained constant or diminished (3, 13-15, 17).

Most of the available data from local or regional surveys are cross-sectional. Generally, these data have shown consistent increases in use with age, although in some areas, use appears to peak in the ninth or tenth grade and to decline subsequently (27, 29);³ only limited longitudinal data are available. In Louisiana, cross-sectional surveys of students ages 8 through 18 conducted in 1976 and 1981 showed increases in use of snuff and chewing tobacco over time within age categories, within cohorts, and across age categories (27). In an Oregon study, use of SLT at baseline was the best predictor of use 9 months later (30). Longitudinal data are presented in this issue by Ary (22), Burke et al. (23), and Sussman and co-workers (28). Increases in prevalence were consistently observed within cohorts, with the exception of some older student cohorts. For example, Ary (22) provides follow-up data that indicate considerable stability in use practices.

The age of initiation is considerably younger than would have been predicted from studies of other substances that may be abused (table 2).

In other studies, substantial rates of use have been reported among fourth-grade students in several areas of the country (19). Similarly, Peterson et al. (34) provide retrospective data on the initiation of SLT use, which indicate 15.1% of tenth graders had tried it by the age of 10 and 4.2% were using it on a weekly basis by this age.

CORRELATES OF ADOLESCENT SUBSTANCE USE

Correlates of health-compromising behaviors such as cigarette smoking, alcohol consumption, and other drug use have been extensively studied during the past decade. An understanding of these correlates, especially with regard to the onset of such behaviors, has provided the principal rationale for intervention development efforts targeting primary prevention (35, 36). Although far less is currently known regarding the correlates of SLT use, previous work related

to other substances will undoubtedly serve as a guide to current and future research in this area.

Despite differences among the various substance use behaviors that have been studied, important similarities have emerged. Although no real consensus exists with respect to etiology, some agreement has developed regarding a common underlying theoretical framework and a common set of underlying factors that predispose adolescents to substance use (37). This framework has borrowed considerably from the perspectives of the social learning model of Bandura (38), the problem behavior theory of Jessor and Jessor (39), the attitude change model of Ajzen and Fishbein (40), and the peer influence concepts of Festinger (41). Within this context, health-compromising behaviors are conceptualized as socially learned, purposeful, and functional activities that are determined through the interplay of a variety of external and intrapersonal factors. These factors serve to shape behavioral responses through combinations of positive and negative reinforcement (38).

The onset of substance use typically occurs during adolescence, and the initial use of tobacco, alcohol, or other drugs tends to be confined to social situations (42). Of the many variables that have been studied as possible correlates of initial substance use, several have shown more consistent significant relationships. Because of the role that these factors are thought to play in the acquisition of other substance use behaviors, each should be considered as a potential correlate of SLT use.

Social Influences

The influence that others can exert upon an individual in the context of a social interaction has been shown to be one of the most salient predictors of substance use onset among adolescents (43). The primary factors of this type include family influences and peer influences. However, the importance of these two categories of influences is believed to vary across substances. Adolescents whose parents drink alcohol are more likely to use hard liquor and certain illicit drugs other than marijuana. For cigarettes and marijuana, on the other hand, the major social influence predicting individual use is having a friend who uses the same substance (44, 45). Adolescents' perceptions of the attitudes of parents and peers toward substance use, specifically with regard to approval or disapproval, also has an effect on the acquisition of such behaviors (46, 47). As children pass through childhood into adolescence, parental influences are thought to change, exerting their greatest effect during the preadolescent years. This is a time when health-related knowledge, beliefs, attitudes, values, and early intentions are formulated as part of what has been termed a behavioral "preparation" stage (48). As children approach adolescence, this progressive decline in the importance of parental influence accompanies a corresponding increase of salience of peer influences and other factors related to extrafamilial socialization (49). Although these factors are highly correlated with the onset of substance use, the interrelationships between familial and extrafamilial social influences are highly complex, and the relative importance of these variables varies across substances and at different points during adolescent development (50).

TABLE 2.—Age of initiation of regular SLT use among representative groups

Area	Reference	Reported age at initiation, yr	SLT users	
			Student group	Percent
Arkansas	(31)	<4-5	Kindergarten	21
Texas	(32)	<12	Junior/senior high school	55
Oklahoma	(21)	<10	Kindergarten-high school	33-50
Rhode Island	^a	~9	High school	18
Atlanta, Georgia	(33)	12	Junior/senior high school	50
Southeastern United States	(18)	<10	Kindergarten-fourth grade	0.3

^a Mariciano LA: Personal communication.

Self-image and Personality Traits

Self-image variables also have been studied as potential influences on the development of youths' intentions to experiment with health-compromising behaviors (51, 52). Early adolescence is a period of development during which individuals gradually establish a sense of autonomy through a process that typically involves a considerable amount of behavioral experimentation, and, for certain individuals, this experimentation includes substance use. In fact, Jessor (46) has suggested that experimentation with tobacco, alcohol, and other drugs provides a major focus for some children in the process of developing a sense of personal identity. For these children, many of whom perceive themselves as unsuccessful in meeting adult expectations, self-image factors may exert a greater effect on their behavior than peer pressure or other social influences (43).

Other variables that have been studied in the context of self-image and its relationship to substance use include external locus of control, low self-esteem, low self-satisfaction, a need for greater social approval, low self-confidence, high anxiety, low assertiveness, impulsiveness, and rebelliousness (35, 38, 53). The evidence supporting some of these constructs as predictors of substance use, however, is difficult for some (54-56) to interpret and, at times, conflicting. This is most likely due to a tendency for these traits to vary to some extent across subgroups of individuals and across the time span of adolescent development.

Cognitive and Affective Factors

Researchers' attempts to understand the antecedents of substance use behaviors have resulted in the identification of a variety of psychologic factors that have been extensively studied to date. The major impetus for this research came from the realization that prevention programs that focus only on educating adolescents regarding the legal, pharmacologic, and medical consequences of substance use were virtually ineffective in deterring onset (57, 58). Consistent with conceptual approaches to behavior that have developed concurrently (38, 40), different categories of variables have been studied as potential correlates of substance use behaviors. These categories, which include factors such as knowledge, beliefs, values, attitudes, and intentions, have been combined in various conceptual models by behavioral scientists attempting to rationalize the behavior change process as it relates to substance use (48, 59). These different factors are likely to be related to behavior, but their interrelationships are highly complex and poorly understood.

Multiple Substance Use and Other Behaviors

The use of specific substances has been shown to be correlated with the use of other substances (60) and with other health-related behaviors (61). For example, individuals who smoke cigarettes are more likely to drink alcohol or to smoke marijuana than are nonsmokers of tobacco (62). In fact, individuals who experiment with more than one substance have been reported to do so in a predictable sequence that has been referred to as a substance use hi-

erarchy (47). This sequence typically begins with the use of cigarettes and alcohol followed by marijuana. The use of other drugs such as stimulants and depressants generally follows later and precedes the use of "harder" drugs like opiates, cocaine, and their derivatives (63). Although the causal relationships between the use of one substance and that of another are poorly understood, it is clear that the use of health-compromising substances that are perceived as "less harmful" could potentially facilitate experimentation with more dangerous substances (63).

It also has been shown that the use of tobacco, alcohol, and other drugs is correlated with a variety of other health-compromising behaviors. These behaviors include poor school performance as measured by low grades and absenteeism (39), premature sexuality and psychosocial risk-taking (46), various acts of delinquency and rebellion (47), and antisocial behaviors such as lying, cheating, and stealing (64).

CORRELATES OF SMOKELESS TOBACCO USE

Although SLT use has been far less extensively studied than the use of other substances, preliminary research suggests that, in general, the process of becoming a user is similar in certain respects to the process of becoming a cigarette smoker. For example, social influences appear to be important factors in the onset of its use. A number of studies have reported that users are more likely than nonusers to have friends who also use (30, 65-67).

This relationship also has been reported for current nonusers who intend to use (68). In addition to these reported peer influences, Gritz et al. (65) noted that users were more likely than nonusers to have fathers who also use, which suggests the potential importance of parental influence as well.

None of these investigators, however, attempted to define the specific roles that peer or family influences play in determining the initiation of SLT use nor did they report these data in correlations. In one study that did report results in percentage of explained variance, the social influences variables found to explain use significantly were: peer use, father's approval, and mother's approval (69).

Young and Williamson (31) have reported data that also suggest that early family influences could have a significant effect on the onset of use. In a sample of 112 kindergarten children interviewed, 21.4% reported that they had already used SLT and an additional 35.7% expected to do so in the future. The variables related to social influences that were significantly correlated with use and expected use in this study were knowing someone who uses and having seen the product used at home. In a retrospective study of adults attending a dental clinic in Ohio, an interaction was noted between age of initiation and social influences. Those who began before age 15 were more likely to have family members who also used SLT than were those who began after age 15 (70). Additional data on the relationships between family and peer influences and use are discussed by several investigators (22, 23, 71).

Previous investigations have provided relatively little information regarding the relationships between self-image or personality variables and SLT use. In a study by Chassin

et al. (72), the image that adolescents associate with its use was analyzed by their using semantic differential ratings of three types of stereotyped teenage models: an athlete, a cowboy, and an average teenager. The social image associated with such use was reported to be more positive than that associated with cigarette smoking. The authors suggested that the adoption of the snuff and chewing tobacco habit has perceived social image benefits for adolescent males. However, this study did not provide a prospective assessment of the value of self-image measures as predictors of SLT use.

Schaefer and co-workers (32) reported that in a survey of 5,392 Texas school children, 9% reported regular use of SLT. Of these, 27% indicated that they used it because friends influenced them and 20% because they wanted to look grown-up. Overall, 47% believed that there were positive social reasons for taking up the habit. In addition, this survey asked respondents to indicate whether advertisements for SLT influenced teenagers to initiate use, and 42% indicated that they did believe that advertisements were influential. Other aspects of advertising practices and product availability are discussed in this monograph (62, 73).

Cognitive factors and their relationship to snuff and chewing tobacco use have been described by a number of studies. For example, Glover (21) reported that only 44% of a sample of 5,392 school children in Texas believed that SLT is harmful to one's health, whereas 77% of these children believed that cigarette smoking is harmful. This general belief that its use is less harmful than cigarettes has been reported in other studies as well (72). With regard to knowledge of specific harmful effects, Schaefer et al. (32) reported that 67% of their sample believed that dipping and chewing of tobacco could cause cancer.

Other studies have reported conflicting results. For example, Marty and co-workers (74) reported that neither users nor nonusers could consistently identify the health risks associated with it, although the risks associated with smoking cigarettes were accurately delineated by both groups. Females in this study were more likely than males to believe that SLT had at least a moderate effect on one's health. In a similar study by Marty, McDermott, and Williams (75), only 31% of the respondents could identify the specific health consequences associated with SLT use from among a list of six options presented. In this monograph, Bauman et al. (70) examine the relationship between adolescent use and perceived risk.

The relationship between SLT and other substance use has been described in a number of studies. In a survey of Arkansas high school students (74), only a modest level (28.2%) of individuals reported using cigarettes and SLT, but 70.7% reported using both alcohol and SLT. Other studies have reported significant correlations between use of SLT and alcohol, marijuana, and other drugs (20, 30, 67, 76). Similarly, in this volume, several authors report that the use of other substances, when assessed, was consistently observed to correlate with SLT use (22, 23, 28, 34).

Because of the significant health risks associated with cigarette smoking, correlations between the use of SLT and smoked tobacco should be of special concern to health professionals. Various correlations of this type have been observed. Some have suggested, for example, that SLT is

used by adolescent males as a perceived "safe" alternative to cigarettes (72). Chassin et al. (68) observed higher rates of its use among adolescent ex-smokers than among any other group. Glover and associates (77) found three times as many ex-smokers using SLT as ex-SLT users who smoked cigarettes in a North Carolina college student population. Perceived health risk of cigarette smoking was the reason most often cited for changing to snuff and chewing tobacco.

In addition to its role as one of the sequelae of cigarette smoking, SLT use is also a potential precursor to, or a risk factor for, cigarette smoking. Several investigators suggest that SLT experimentation precedes that of cigarettes among some children (21), and SLT may be preferred to cigarettes by the younger age groups (29).

Considerable variability, however, can be observed among studies in the degree of observed correlation between cigarette smoking and SLT use. For example, in Louisiana, Hunter et al. (27) found little overlap between the two practices and few adolescents who used both products. Others (22, 23, 34, 76) have found considerable overlap with as many as 70% of the smokers also reporting SLT use (21, 68).³ This finding may reflect regional differences, or, as data from Oregon suggest, an age effect (66). Lichtenstein and co-workers reported a strong association between use of cigarettes and SLT among seventh graders, but the relationship was weaker among ninth graders and was reversed among children in the tenth grade. Peterson et al. (34) found the rates of onset for regular use of SLT and cigarettes to be identical before age 11 and to diverge subsequently.

Longitudinal studies indicate a reciprocal relationship between smoking and SLT use. Hunter and associates (27) found that, over a 5-year period, decreases in its use were accompanied by increases in cigarette smoking. In 1981-1982, the prevalence of smoking among 16-year-olds was twice that of 14-year-olds, but use of snuff was only one-half as prevalent. In a 9-month follow-up study (78), cessation of SLT use was associated with a high cigarette smoking rate and intention to smoke cigarettes. The authors cautioned that their sample size was small, however, and that the relationship was suggestive at best. In a separate 9-month follow-up study by the same investigators, use of SLT was found to be a risk factor for the onset and/or increased use of cigarettes, as well as for marijuana and alcohol use (30). Burke et al. (23) reported that between 1980 and 1985 a decrease in weekly smoking by seventh-grade boys was correlated with an even greater increase in the use of SLT.

The Surgeon General has concluded that nicotine present in cigarettes and other forms of tobacco causes addiction and that the underlying processes of this addiction are similar to those that determine it to other drugs such as heroin and cocaine (79). Because users of SLT sustain significant blood nicotine levels (9-12), nicotine addiction must be considered one potential adverse health consequence from its use. Users often report subjective dependence (14, 80, 81) and have been found in laboratory settings to experience withdrawal symptoms during abstinence similar to those of abstinent cigarette smokers (3, 82). In this monograph, a unique study reporting data from a cessation clinic

for SLT dependence found that 20% of the adolescents enrolled in the intervention program were abstinent at 6 months (83). This success rate is comparable to that observed in smoking cessation clinic programs and suggests that the difficulty a person experiences in attempting to quit using SLT may also be comparable.

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Smokeless Tobacco: Association With Increased Cancer Risk

Margaret E. Mattson¹ and Deborah M. Winn^{2, 3}

ABSTRACT—Smokeless tobacco (chewing tobacco and snuff) contains known carcinogens shown to increase the risk for oral cancer. The effect of snuff has been more fully documented than other forms of smokeless tobacco, although the carcinogenic potential of all such products is acknowledged. Risk increases with increasing length of exposure, with risks greatest for anatomic sites where the product has been held in contact the longest time. In some studies, other organs, such as the esophagus, larynx, and stomach, have been shown to be at increased risk for cancer from the use of smokeless tobacco, although at present the data are insufficient to substantiate fully a causal association. Numerous reports have shown an association between snuff use and leukoplakia, with less evidence at present linking chewing tobacco use with leukoplakia. The documented early onset of the smokeless tobacco habit and reports of increases in certain oral cancers among young men raise serious concerns of an impending oral cancer epidemic in this population. In addition, synergistic interactions with other oral cancer risk factors, e.g., smoking and alcohol, and a high rate for second primaries observed for these cancers add to the concern. Unless the tide of its use is stemmed, long-term use can be expected to produce an increase in oral cancers, and perhaps cancers of other sites, as youthful users mature and accumulate exposure to this carcinogenic agent.—NCI Monogr 8:13-16, 1989.

Increased risk for oral cancer has been associated with the use of chewing tobacco and snuff or SLT. The recent rise in its use, especially among youth, prompted four consensus conferences between 1984 and 1987 in the United States and Europe to evaluate, critically and systematically, the data supporting this relationship (1-4). The remainder of this monograph documents this upsurge in the use of SLT. In this paper, we discuss the implications of these trends in the light of the body of research evidence on SLT and cancer. The conclusions from these four consensus meetings are summarized, additional evidence published since these reports were presented are cited, and this evidence is related to features of the new epidemic of SLT use that may have a bearing on the incidence of oral cancer in the coming decades.

The focus of this summary will be on cancers, particularly oral cancers, and potentially precancerous conditions,

such as leukoplakia. The consensus reports have also presented substantiations of an association of SLT use with gingival recession, both local and generalized. Evidence related to other diseases such as periodontal disease and tooth decay was examined as well. However, although these conditions are also important potential sequelae of SLT use, the emphasis in this review is on epidemiologic evidence for increased cancer risk in humans.

The general conclusion reached by the consensus conference groups is that the risk for oral cancer is increased as a result of SLT use. The effect of snuff has been more fully documented than other forms, although the carcinogenic potential of all SLT products is acknowledged. Risk increases with increasing length of exposure, with risks greatest for anatomic sites where the product has been held in contact the longest time. In some studies, other organs, e.g., esophagus, larynx, and stomach, have been shown to be at increased risk for cancer from the use of SLT, although at present the data are insufficient to substantiate fully a causal association. Numerous reports have shown an association between snuff use and leukoplakia, with less evidence at present linking chewing tobacco use with leukoplakia.

Cigarette smoking and alcohol use are well-documented potent risk factors for oral cancer (5, 6); together they account for about 74% of the oral and pharynx cancers in the United States (6). The proportion of cancer cases attributable to a risk factor is a function of the magnitude of the association and the extent of exposure to the risk factor, and so the estimate will be sensitive to current and future SLT use patterns. There is no general acceptance of any one estimate of the proportion of all oral cancer cases attributable to its use. However, overall, approximately 29,800 new cases of oral cancer, or about 3% of total new cancers, were expected for 1987, with the majority occurring in males. The estimated number of deaths for 1987 was 9,400 or about 2% of total cancer deaths. The age-adjusted incidence rate (1981-1985) is 11.5 for whites and 14.5 for blacks, with the male differential pronounced across races, i.e., 16.9 for whites and 23.6 for blacks (7).

Clinicians agree that cancer stage at detection is the most influential factor determining length of survival and that "no lethal disease is easier to cure than oral cancer of less than 1 cm in diameter" (8). Hence the frustration that, despite the relative accessibility of the mouth for examination compared with other sites, at diagnosis most oral cancers are large, symptomatic stage III and IV lesions, with 50% of the patients having metastatic lymphadenopathy (8). Despite surgery, radiation therapy, and chemotherapy, overall survival rates for cancers of the oral cavity and pharynx are 53% for white males and 26% for black males (7). Even with modern reconstructive techniques, the impact upon

ABBREVIATION: SLT = smokeless tobacco.

¹ Division of Cancer Prevention and Control, National Cancer Institute, Executive Plaza North, Room 330, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892. Address reprint requests to Margaret E. Mattson, Ph.D.

² Division of Health Interview Statistics, National Center for Health Statistics, Hyattsville, MD.

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quality of life for patients with advanced and disfiguring head and neck cancer may be devastating. Those who survive oral or pharynx cancer have an exceptionally high risk of developing subsequent cancers. As many as 9% of the patients with cancer of the tongue, 14% of those with other mouth cancers, and 8% of the patients with pharynx cancer develop a second primary cancer.

CARCINOGENS IN SMOKELESS TOBACCO

Chemical analyses of SLT indicate that three types of known carcinogenic agents are present: N-nitrosamines, polycyclic aromatic hydrocarbons, and polonium 210, a radioactive alpha-emitter. Nitrosamines are present in SLT at levels 100 times higher than the levels of these substances in food, such as bacon, that are regulated by law. The nitrosamines are metabolized *in vivo* to products shown to produce genetic changes in cells and also produce tumors, benign and malignant, in animals when applied in amounts comparable to a human lifetime exposure dose for regular SLT users (1-3). The nitrosamine content of snuff may be 10-100 times greater than the level received by a smoker of one cigarette (9).

Because of the high levels present and their ability to induce cancerous lesions, the nitrosamines are probably the major contributor to the carcinogenic potential of SLT. At present, cancer has been induced in animals by application of the carcinogenic chemical but not by exposure to actual SLT products. Deficiencies in design or execution of many of the studies may account for the absence of an observable effect. Several recent studies indicate that infection with herpes simplex virus may play an interactive role in the carcinogenic process, because animals infected with the virus do develop malignant and premalignant changes when exposed to SLT products. This issue deserves more research attention, because 20%-40% of the United States population has episodes of labial herpes and even more carry the virus without expressing it (10).

SNUFF AND CANCER

The strongest data associating the use of SLT with cancer are provided by studies that link "snuff dipping" or oral use of snuff to cancers of the oral cavity. Many of the early studies on this association made no distinction between snuff and chewing tobacco and some did not control for cigarette use (11). However, the case-control studies and case series that make clear the distinction between snuff and chewing tobacco provide sufficient evidence that oral use of snuff is carcinogenic (2). Across several studies conducted in the South, where snuff dipping has been popular among adults, the percentage using snuff varied from 11 to 40, with even higher rates in some subgroups, compared with only a few percent in disease-free controls (11).

Winn et al. (12) undertook a landmark study in North Carolina in which they overcame many previous methodologic problems and substantiated earlier conclusions. These authors found that, among female nonsmokers, the risk of oral cancer was 4.2 times greater for those who used snuff than for those who did not, with the cancer risk greatest in the parts of the mouth where the snuff was habitually placed. The risk increased with longer duration of

use, reaching a relative risk of 48 for cancer of the gum and buccal mucosa among users of snuff for over 50 years. The authors calculated that 87% of the cancers of the gingival and oral mucosa in the southeastern United States population were due to snuff use. A more recent case-control study conducted by the National Cancer Institute with four population-based cancer registries also found a substantial oral cancer risk associated with snuff or snuff and chewing tobacco combined; however, this risk could be quantitated only in the few women study subjects who did not smoke (6).

CHEWING TOBACCO AND ORAL CANCER

The epidemiologic evidence for the carcinogenicity of chewing tobacco is presently less convincing primarily because of methodologic shortcomings, i.e., questionable validation of use, failure to control for smoking, and failure to provide dose-response data. Evidence for a positive association was provided by two of the five available case-control reports (13, 14), although no control was provided for cigarette smoking in either study. One study (15) that did control for smoking found an odds ratio of 12 for oral cancer among chewers versus nonchewers; however, these results were not confirmed in the study by Wynder and Stellman (16) that also controlled for cigarette smoking. Because chewing tobacco also contains the same carcinogenic N-nitrosamines as snuff (1), Winn speculates that the reason for the lack of agreement among findings may occur because most forms of chewing tobacco are, in fact, chewed. Because of movement in the mouth and increased salivation, physical contact between the tobacco and oral mucosa is not maintained as intensely as for snuff, which is usually maintained in one spot (11). Thus the proximity of tissues to the tobacco and duration of direct contact may be factors of some significance.

SMOKELESS TOBACCO AND OTHER CANCERS

Data on humans are insufficient for researchers to conclude that SLT causes cancer at nonoral sites. However, limited but suggestive data exist to raise the possibility of the carcinogenic potential of snuff at other aerodigestive sites where exposure is direct and prolonged, such as the esophagus, supraglottic larynx, and stomach. Nasal use of snuff has been associated with increased nasal cancer in studies in the United States, the United Kingdom, other European countries, and Africa (1, 10). In the United States, a 50% excess risk associated with snuff use was found in a case-control study of nasal cancer with increased risks observed for adenoid and squamous carcinomas (17). A case report described squamous cell carcinoma that developed in the ear of a man who placed snuff in his ear for 42 years (18).

It appears that the risk for bladder cancer in users is not increased; results for kidney cancer are inconsistent. At present, insufficient epidemiologic evidence exists for one to evaluate conclusively the relationships, although several studies have shown an increased risk (10). Investigators need to conduct studies of sufficient size to detect small effects and to control for potentially confounding variables.

ASIAN SMOKELESS TOBACCO PRODUCTS

The highest rates of oral cancer in the world are found in India, where oral cancer is the most common tumor (1, 2). Tobacco use is widespread in this country with between 47% and 73% of the population using some form of tobacco including cigarettes, cigars, and chewing (19). The inclusion of lime, areca nut, and other ingredients in many of the SLT-containing products of India hinders the evaluation of the contribution of tobacco per se to the increased risk of oral tumors found in this country. However, it is believed that none of these additives has more than a small direct carcinogenic effect on oral tissues and that the high rate of malignant transformation in groups who chew these products is due to the presence of tobacco. Indeed, an evaluation of 5 studies of oral cancer among chewers of betel quid with or without tobacco bears this out (1). Users of tobacco-containing products had substantially higher oral cancer risks compared with users of non-tobacco-containing quid. Confounding from cigarette smoking was also ruled out in these studies. The report concludes that the habit of quid chewing accounts for most of the oral cancers in the diverse populations studied, which included Calcutta, Madras, Karachi, Bombay, and several other areas of India and Sri Lanka.

SMOKELESS TOBACCO AND LEUKOPLAKIA

In studies in the United States and Scandinavia, between 8% and 59% of the SLT users were found to have oral leukoplakia (10). Lesions are commonly found at the habitual site of tobacco placement, and long-term duration of the habit and daily intensity of use are determinants of the severity of the leukoplakias. Quantitative estimates of the risk for malignant transformation are difficult for researchers to obtain, but an apparent consistent finding is that tobacco-induced leukoplakias can develop into cancer over a period of years (10).

In a large series of over 23,000 white Americans over 35 years of age, 3.4% on examination had white keratotic changes of the mucosal surface, 86% of which were leukoplakias (20). Twenty-five percent of the individuals with leukoplakias underwent biopsies; of these, about one-quarter of them were demonstrated to have either early invasive carcinoma or severe epithelial dysplasia. If the overall rate of cancerous leukoplakias was the same as the rate in the biopsy specimens, 168 cases or 0.7% of the population had cancers.

COMMENT AND CONCLUSION

The data on carcinogenic effects of SLT, particularly snuff used orally, are convincing and sufficient to arouse public health concern over the growing use of this product by youth. Additional features of this growing use are especially disturbing.

- 1) Hospital case reports and registries (21, 22) and national data (23, 24) show an increase in tongue cancer among younger males under 40. Although differing opinions exist (21, 25), this increase may be related to the rise in SLT use among young men and may be the harbinger of an impending oral

cancer epidemic in this population. It reinforces the need for both close monitoring of the oral condition of young current users as well as former users and active education and prevention programs.

- 2) If this epidemic of oral cancer among the young materializes, the high rate of second primaries often observed in later life for these types of cancers (26) becomes a matter of serious concern in the survival of this population.
- 3) The potential for synergistic interactions with other oral cancer risk factors may be enhanced by the tendency of youthful SLT users also to smoke cigarettes and drink alcohol and for users without these other habits to adopt them with greater frequency than nonusers (27, 28).
- 4) The strong relationship between oral cancer risk and duration of SLT use seen in studies of older persons with oral cancer implies that the early onset of the SLT habit in today's youth, and thus the opportunity for sustained exposure, is a matter of serious concern. Its use in a kindergarten population has been reported (29), and use before junior high school is common (30).
- 5) Most of the epidemiologic research on SLT was done with users of "dry" snuff, whereas the most popular form among young users today is moist snuff. Chemical analysis reveals that both types have the same carcinogenic potential (31).
- 6) Studies of youthful users show that soft tissue lesions and leukoplakias are not infrequent (1). Long-term follow-up studies are not available, and the magnitude of malignant transformation is unknown, although regression of lesions with discontinuance of use has been observed (1).

The present evidence is cause for a serious public health alarm that, unless the tide of SLT use is stemmed, long-term use can be expected to produce an increase in oral cancers, and perhaps cancers of other sites, as youthful users mature and accumulate exposure to this carcinogenic agent.

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Use of Smokeless Tobacco in the United States: Recent Estimates From the Current Population Survey¹

Alfred C. Marcus,² Lori A. Crane,² Donald R. Shopland,³ and William R. Lynn³

ABSTRACT—Chewing tobacco, snuff, and total smokeless tobacco use from the 1985 Current Population Survey (CPS) are reported. The CPS is the only survey capable of providing national, regional, and individual state tobacco use estimates for all 50 states and the District of Columbia. The prevalence of smokeless tobacco use varies considerably among and within regions of the country, by division and state. Smokeless tobacco use is highest in the South and lowest in the Northeast. Individual states with the highest smokeless tobacco use among males are West Virginia (23.1%), Mississippi (16.5%), Wyoming (15.8%), Arkansas (14.7%), and Kentucky (13.6%). In all regions of the country, use of smokeless tobacco among women is considerably less than men. Nationally, male use of such products was 5.5%; less than 1% of women use them. Snuff consumption is predominantly a behavior characteristic of white males; less than 1% of black or Hispanic males consume this product. Higher percentages of blue-collar and service workers use it compared with white-collar workers. Snuff and chewing tobacco use among teenage boys in the United States increased dramatically between 1970 and 1985, a time when their use of cigarettes was declining. The significance of individual state level estimates is discussed.—NCI Monogr 8:17–23, 1989.

Periodic national surveys for tobacco use assessment have been sponsored by numerous agencies and institutes within the United States Public Health Service. Most of these national surveys have focused on smoking behavior, with only limited attention given to the use of SLT. The first large-scale survey of tobacco use was conducted by the National Cancer Institute in 1955, when detailed questions about cigarette and pipe and cigar smoking were added to the CPS. This survey did not include questions on the use of chewing tobacco or snuff. Similarly, although the National Center for Health Statistics has collected limited data on cigarette smoking as part of the ongoing National Health Interview Survey, these surveys have not collected information routinely on other forms of tobacco use.

When the National Clearinghouse for Smoking and

Health (now the Office on Smoking and Health) was established after the release of the first report of the Surgeon General on smoking (1), several surveys on adult use of tobacco were conducted that included questions on other forms of tobacco use, including patterns of chewing tobacco and snuff use. However between 1966 and 1986, only 4 such surveys were conducted.

Beginning in the early 1980s, the attention of the public health community began to focus on the use of SLT as a significant public health problem. At that time, it became apparent that both national and regional data on its use were urgently needed. In 1985, one of the authors (DRS), while serving as Acting Director of the Office on Smoking and Health, approved funding for a short series of questions about cigarette smoking and use of other tobacco products (snuff, chewing tobacco, pipe and cigar smoking) to be added to the September 1985 CPS. Information on tobacco use was collected from 114,342 individuals. The large sample size of the CPS provides a unique opportunity for researchers to examine national, regional, divisional, and state estimates for all forms of tobacco use. The focus of this paper is on SLT use in the United States.

METHODOLOGY

The CPS is a continuous survey conducted monthly by the Census Bureau primarily as a means to assess changes in the labor force for the civilian noninstitutionalized population. The 1985 CPS sample was initially selected from the 1980 census files with coverage in all 50 states and the District of Columbia. The 1985 sample was located in 729 areas comprising 1,973 counties, independent cities, and minor civil divisions in the nation. Of the approximately 62,500 occupied households that were eligible for interview, visits to about 2,500 occupied units (4%) resulted in no completed interviews because the occupants were not found at home (after repeated contacts), they refused to be interviewed or were otherwise unavailable for interview. Although all household members were enumerated, a tobacco use history was obtained only for those individuals 16 years of age or older at the time of interview.

With the use of a special weighting algorithm developed by the Census Bureau, the CPS household sample estimates are considered to be representative of the United States. However, one potential drawback with the CPS is the effect of proxy reports on sample estimates that is presumed to result in a modest underreporting bias. Overall, approximately 55% of the total CPS sample consists of self-respondents, whereas the remaining 45% of the data represents proxy re-

ABBREVIATIONS: SLT = smokeless tobacco; CPS = Current Population Survey; CI = confidence interval(s).

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²Division of Cancer Control, Jonsson Comprehensive Cancer Center, 1100 Glendon Ave., Suite 711, Los Angeles, California 90024. Address reprint requests to Alfred C. Marcus, Ph.D.

³Smoking, Tobacco, and Cancer Program, Division of Cancer Prevention and Control, National Cancer Institute, Bethesda, Maryland.

sponses. The suspected underreporting bias should be most evident for the younger age groups (e.g., 16-19 yr), because they have a higher proportion of proxy responses. In addition, it is conceivable that the proxies for younger respondents included in the CPS (e.g., parents) may be less knowledgeable or aware of SLT use, especially if they do not approve of such use among adolescents and younger adults living in the household.

Two questions were asked in the CPS so that current use of SLT could be determined. For those individuals for whom "yes" was recorded for the question, "Does (name) presently use any other form of tobacco, such as snuff or chewing tobacco?", a follow-up question asked, "What other form(s) of tobacco does (name) presently use?" The categories of snuff, chewing tobacco, cigars, pipe tobacco, or other were coded in response to this follow-up question.

Given the substantial sample size of the CPS (~114,000 records), rates of SLT use are reported by type of product (snuff or chewing tobacco) separately by region, division, and state. Using formulas provided by the Census Bureau (which take into account the multistage sample design of

the CPS), we calculated the 95% CI for each estimate and include them here. Detailed data are only presented for males; less than 1% of females use these tobacco products (0.5% and 0.2% of the women reported using snuff and chewing tobacco nationally, respectively).

RESULTS

Differences by Region, Division, and State

As indicated in table 1, the overall prevalence rate for males is estimated at 1.9% for snuff and 3.9% for chewing tobacco. Use of SLT among males was lowest in the Northeast and highest in the South, with the North Central and West ranking intermediate. Within the Northeast region, both the New England and the Mid-Atlantic divisions had relatively low reported use, but prevalence rates among males in the North Central region approximated the national average for snuff (2.1%) and chewing tobacco (3.4%).

In the South, use of snuff (2.7%) and chewing tobacco (6.0%) exceeded the national average among males. For

TABLE 1.—Percent current users of snuff and chewing tobacco by region, division, and state: ≥ 16 -yr-old males^a

Area	Snuff		Chewing tobacco		Any smokeless		Area	Snuff		Chewing tobacco		Any smokeless	
	Percent	CI	Percent	CI	Percent	CI		Percent	CI	Percent	CI	Percent	CI
United States	1.9	0.2	3.9	0.3	5.5	0.4	Washington, DC	0.0	0.0	0.4	1.0	0.4	1.0
Northeast	1.0	0.3	1.4	0.4	2.3	0.5	Virginia	2.3	1.9	6.2	3.1	7.8	3.5
New England	0.4	0.4	0.8	0.6	1.2	0.8	West Virginia	11.5	4.4	13.5	4.8	23.1	5.9
Maine	0.9	1.3	1.5	1.7	2.3	2.1	North Carolina	1.8	1.0	8.6	2.1	9.8	2.2
New Hampshire	1.2	1.7	1.5	1.9	2.7	2.5	South Carolina	0.7	1.1	5.3	3.0	6.1	3.2
Vermont	0.9	1.4	4.7	3.2	5.5	3.5	Georgia	1.4	1.6	7.3	3.4	8.7	3.7
Massachusetts	0.2	0.3	0.4	0.5	0.5	0.5	Florida	1.1	0.7	1.9	0.9	2.9	1.1
Rhode Island	0.5	1.1	0.6	1.2	0.9	1.5	East South Central	2.7	1.1	9.4	1.9	11.6	2.1
Connecticut	0.3	2.3	0.5	2.9	0.8	1.2	Kentucky	3.2	2.4	11.2	4.4	13.6	4.7
Mid-Atlantic	1.2	0.4	1.6	0.5	2.7	0.7	Tennessee	1.7	1.8	9.3	4.1	10.3	4.2
New York	0.5	0.4	1.2	0.6	1.6	0.7	Alabama	1.7	2.0	6.6	3.9	8.3	4.3
New Jersey	0.1	0.2	0.6	0.5	0.7	0.6	Mississippi	5.7	3.3	11.4	4.5	16.5	5.3
Pennsylvania	3.0	1.2	2.9	1.2	5.6	1.6	West South Central	4.0	1.0	5.5	1.1	9.1	1.4
North Central	2.1	0.5	3.4	0.6	5.3	0.7	Arkansas	6.0	3.4	9.5	4.2	14.7	5.1
East North Central	1.8	0.5	2.9	0.6	4.4	0.8	Louisiana	2.5	2.2	5.8	3.2	8.0	3.8
Ohio	2.2	1.0	3.2	1.3	5.0	1.6	Oklahoma	4.8	2.9	6.7	3.4	11.0	4.2
Indiana	2.6	1.8	3.2	2.0	5.6	2.6	Texas	4.0	1.4	4.6	1.5	8.2	2.0
Illinois	1.1	0.8	2.5	1.1	3.3	1.3	West	1.4	0.4	3.3	0.6	4.5	0.8
Michigan	0.8	0.6	2.7	1.2	3.4	1.3	Mountain	2.3	1.1	5.4	1.6	7.5	1.9
Wisconsin	2.9	2.3	2.9	2.3	5.8	3.1	Montana	5.5	3.1	8.3	3.7	13.7	4.7
West North Central	2.9	1.0	4.7	1.3	7.5	1.6	Idaho	2.3	2.1	6.7	3.5	8.7	3.9
Minnesota	3.5	2.5	2.8	2.2	6.1	3.2	Wyoming	3.4	2.8	13.0	5.2	15.8	5.7
Iowa	1.8	1.9	4.6	2.9	6.4	3.4	Colorado	1.2	1.6	6.4	3.6	7.5	3.9
Missouri	3.1	2.1	3.6	2.2	6.7	3.0	New Mexico	5.3	3.0	5.2	3.0	10.2	4.1
North Dakota	6.1	3.1	5.1	2.9	10.7	4.0	Arizona	2.0	2.1	3.8	2.8	5.4	3.4
South Dakota	1.9	1.7	6.1	3.0	7.9	3.4	Utah	0.9	1.3	3.0	2.4	3.7	2.7
Nebraska	1.4	1.6	6.8	3.4	8.0	3.6	Nevada	1.5	2.0	2.8	2.7	4.3	3.3
Kansas	3.3	2.5	8.6	3.9	11.7	4.4	Pacific	1.0	0.4	2.6	0.7	3.4	0.8
South	2.7	0.5	6.0	0.7	8.3	0.8	Washington	1.8	1.9	6.1	3.5	7.1	3.7
South Atlantic	1.8	0.5	5.2	0.9	6.7	1.0	Oregon	2.7	2.5	5.4	3.4	7.6	4.0
Delaware	0.6	1.2	2.4	2.3	3.0	2.6	California	0.7	0.5	1.7	0.7	2.3	0.8
Maryland	0.4	0.8	2.1	1.8	2.4	1.9	Alaska	2.5	2.2	6.3	3.4	8.8	4.0
							Hawaii	0.2	0.7	0.4	0.9	0.7	1.2

^a Estimates were obtained from the September 1985 CPS.

example, West Virginia reported the highest use of snuff (11.5%) and chewing tobacco (13.5%) in the nation. West Virginia is the only state in the South Atlantic division that exceeded the regional average for snuff. In the East South Central and West South Central divisions, Mississippi (5.7%), Arkansas (6.0%), Oklahoma (4.8%), and Texas (4.0%) also reported relatively high use of snuff (when compared with other Southern states), whereas Mississippi (11.4%), Kentucky (11.2%), Arkansas (9.5%), and Tennessee (9.3%) also reported relatively high use of chewing tobacco. For males, the West had among the lowest rates in the country with respect to snuff use (1.4%) and chewing tobacco (3.3%).

Also reported in table 1 are estimates of "any" SLT use (snuff or chewing tobacco). Of special note in this regard is the finding that rates of any use are largely additive across snuff and chewing tobacco, which indicates little overlap in the use of these tobacco products among males. States reporting exceptionally high rates of any use included West Virginia (23.1%), Mississippi (16.5%), Wyoming (15.8%), Arkansas (14.7%), Montana (13.7%), and Kentucky (13.6%).

Table 2 provides rankings of states with the highest and lowest rates of snuff and chewing tobacco use for males. As shown, states from the South dominate the rankings for high use of both substances; states from the Northeast dominate the rankings for low use of both substances. Interestingly, states ranking high in use of SLT also tend to have a high percentage of nonmetropolitan residents. Thus when we correlated state rates of SLT use (among males) with the percentage of the state population residing outside designated Standard Metropolitan Statistical Areas, we found significant bivariate correlations for snuff ($r=.49$; $P<.001$), chewing tobacco ($r=.60$; $P<.001$), and any use of SLT ($r=.66$; $P<.001$).

Use of SLT is much less prevalent among women in the United States than among men. Overall, an estimated 0.5% of women 16 years of age and over reported using snuff, and they were concentrated almost entirely in the South (1.4%), with all other regions having prevalence rates of 0.1% or less. Southern states with the highest reported use of snuff among women included North Carolina (4.0%), South Carolina (2.2%), Georgia (2.7%), Alabama (2.6%), Mississippi (2.0%), and Tennessee (1.9%). Only one other state in the nation reported a prevalence rate for snuff that exceeded 2.0% among women (Alaska = 2.1%).

Use of chewing tobacco is even less prevalent among women than use of snuff, with an estimated 0.2% prevalence rate nationally. The Northeast, North Central, and West had rates of chewing tobacco use that were 0.1% or less for women. It was highest in South Carolina (1.1%), Mississippi (1.4%), and Arkansas (1.7%). No other state in the nation exceeded a prevalence rate of 1.0%.

Differences by Race or Ethnicity

Tables 3 and 4 depict racial and ethnic differences among males in reported use of SLT. As shown, estimates for the United States show white males reporting noticeably higher rates of using snuff (2.2%) and chewing tobacco (4.3%). Black and Hispanic males are similar in their reported use of snuff, with both groups reporting a much lower rate of 0.7%. With respect to chewing tobacco, black males (2.6%) ranked second to whites and Hispanics (1.1%) ranked third. White males maintain their higher reported use of snuff and chewing tobacco in all regions and divisions within the United States. The use of both among white males was greatest in the South, with the highest rate of snuff use reported in the West South Central division (4.9%) and the highest rate of chewing tobacco use reported in the East South Central division (10.4%).

TABLE 2.—States ranking highest and lowest in use of snuff and chewing tobacco by ≥ 16 -yr-old males

Tobacco product	Highest rates			Lowest rates		
	State	Region	Rate	State	Region	Rate
Snuff	West Virginia	South	11.5	Washington, DC	South	0.0
	North Dakota	North Central	6.1	New Jersey	Northeast	0.1
	Arkansas	South	6.0	Hawaii	West	0.2
	Mississippi	South	5.7	Massachusetts	Northeast	0.2
	Montana	West	5.5	Connecticut	Northeast	0.3
	New Mexico	West	5.3	Maryland	South	0.4
	Oklahoma	South	4.8	Rhode Island	Northeast	0.5
	Texas	South	4.0	New York	Northeast	0.5
	Minnesota	North Central	3.5	Delaware	South	0.6
	Wyoming	West	3.4	South Carolina	South	0.7
Chewing tobacco				California	West	0.7
	West Virginia	South	13.5	Massachusetts	Northeast	0.4
	Wyoming	West	13.0	Hawaii	West	0.4
	Mississippi	South	11.4	Washington, DC	South	0.4
	Kentucky	South	11.2	Connecticut	Northeast	0.5
	Arkansas	South	9.5	New Jersey	Northeast	0.6
	Tennessee	South	9.3	Rhode Island	Northeast	0.6
	North Carolina	South	8.6	New York	Northeast	1.2
	Kansas	North Central	8.6	Maine	Northeast	1.5
	Montana	West	8.3	New Hampshire	Northeast	1.5
	Georgia	South	7.3	California	West	1.7

TABLE 3.—Percent current users of snuff by race, region, and division: ≥ 16 -yr-old males^a

Area	White		Black		Hispanic	
	Percent	CI	Percent	CI	Percent	CI
United States	2.2	0.3	0.7	0.4	0.7	0.5
Northeast	1.2	0.4	0.1	0.4	0.2	0.6
New England	0.5	0.5	—	—	—	—
Mid-Atlantic	1.5	0.5	0.2	0.6	0.2	0.7
North Central	2.3	0.5	0.1	0.4	0.0	0.0
East North Central	2.0	0.6	0.2	0.6	0.0	0.0
West North Central	3.1	1.1	0.0	0.0	—	—
South	3.1	0.6	1.0	0.7	1.6	1.4
South Atlantic	2.2	0.7	0.7	0.8	0.7	1.7
East South Central	2.9	1.2	1.8	2.2	—	—
West South Central	4.9	1.3	1.0	1.4	2.0	1.9
West	1.6	0.5	0.9	1.6	0.3	0.5
Mountain	2.6	1.2	—	—	1.1	2.0
Pacific	1.2	0.5	1.0	1.8	0.0	0.0

^a Estimates were obtained from the September 1985 CPS. Estimates based on fewer than 100 cases (as indicated by dashes) were deleted from the table.

Use of SLT by women was higher among blacks than whites or Hispanics. Overall, 2.1% and 1.2% of black women are estimated to use snuff and chewing tobacco, respectively; the corresponding figures for white women are 0.3% and 0.1%. Among Hispanic women, use of SLT was virtually nonexistent (less than 0.1% for snuff and chewing tobacco). Among black women, use of snuff was estimated at 0.3% in the Northeast, 0.5% in the North Central, 3.5% in the South, and 0.4% in the West. Among white women, use of snuff was estimated at less than 0.1% in the Northeast, North Central, and West, and 0.9% in the South.

With respect to the use of chewing tobacco, prevalence rates for black women were estimated at 0.3% in the North-

east and West, 0.1% in the North Central, and 2.0% in the South. Among white women, rates of chewing tobacco use did not exceed 0.1% in any region of the country except the South where it was 2%.

Differences by Occupation

Occupational differences among males in reported use of snuff follows the same gradient typically found for cigarette smoking (2). Thus male white-collar workers reported lower rates, followed by service and blue-collar workers (table 5). Reported use of chewing tobacco among males shows a similar pattern nationally, with rates of white-collar workers typically being the lowest, followed by service and blue-collar workers (table 6).

Reported use of snuff among females was virtually nonexistent for white-collar workers (0.0%), followed by service (0.4%) and blue-collar workers (0.5%). Use of chewing tobacco was also virtually nonexistent for female white-collar workers (0.0%), compared with 0.4% for female service and blue-collar workers. Use of snuff and chewing tobacco among female service and blue-collar workers was confined largely to the South. One exception to this pattern occurs in the Mountain division of the West, where 0.9% of female blue-collar workers reported using chewing tobacco.

Differences by Age

As reported in table 7, young adults reported higher rates of using snuff, which is especially evident in the South. In contrast, no clear age pattern is observed in use of chewing tobacco among males (table 8), although the oldest age group reported slightly higher usage than did other age groups. In the West, use of chewing tobacco among males was higher in the younger age groups (16–29 yr).

With respect to females, a modest age gradient occurred in use of SLT, with the 70 and over group reporting the highest rates of snuff (2.0%) and chewing tobacco (0.5%)

TABLE 4.—Percent current users of chewing tobacco by race, region, and division: ≥ 16 -yr-old males^a

Area	White		Black		Hispanic	
	Percent	CI	Percent	CI	Percent	CI
United States	4.3	0.4	2.6	0.8	1.1	0.7
Northeast	1.6	0.5	0.7	1.0	0.4	0.9
New England	0.8	0.6	—	—	—	—
Mid-Atlantic	1.9	0.6	0.7	1.1	0.5	1.1
North Central	3.7	0.6	0.6	0.9	2.7	3.7
East North Central	3.2	0.7	0.6	1.0	0.7	2.1
West North Central	4.8	1.3	0.4	1.8	—	—
South	7.0	0.8	3.9	1.3	1.3	1.3
South Atlantic	5.8	1.1	3.6	1.7	0.5	1.4
East South Central	10.4	2.2	4.6	3.4	—	—
West South Central	6.6	1.5	4.1	2.8	1.6	1.7
West	3.9	0.8	2.2	2.5	1.1	1.0
Mountain	5.8	1.8	—	—	2.3	2.9
Pacific	3.1	0.9	2.6	2.9	0.6	0.9

^a See footnote, table 3.

TABLE 5.—Percent current users of snuff by occupation, region, and division: ≥ 16 -yr-old males

Area	Workers					
	White collar		Service		Blue collar	
	Percent	CI	Percent	CI	Percent	CI
United States	1.0	0.3	1.6	0.7	2.8	0.5
Northeast	0.4	0.4	0.5	0.8	1.7	0.8
New England	0.1	0.4	0.8	2.1	0.5	0.9
Mid-Atlantic	0.5	0.5	0.4	0.9	2.0	1.0
North Central	1.1	0.6	1.5	1.4	2.9	0.9
East North Central	0.8	0.6	1.5	1.7	2.4	1.0
West North Central	1.6	1.4	1.7	2.9	4.1	2.0
South	1.4	0.6	2.8	1.8	3.9	0.9
South Atlantic	0.9	0.7	2.3	2.2	2.4	1.1
East South Central	1.2	1.4	3.0	4.9	3.9	2.0
West South Central	2.3	1.3	3.5	3.5	6.3	2.0
West	1.0	0.6	1.2	1.4	1.6	0.8
Mountain	1.7	1.5	1.6	2.8	3.2	2.3
Pacific	0.8	0.6	1.1	1.6	0.9	0.7

TABLE 6.—Percent current users of chewing tobacco by occupation, region, and division: ≥ 16 -yr-old males

Area	Workers					
	White collar		Service		Blue collar	
	Percent	CI	Percent	CI	Percent	CI
United States	2.1	0.4	3.1	1.0	5.2	0.6
Northeast	0.7	0.5	0.8	1.1	2.0	0.9
New England	0.3	0.6	0.7	2.0	1.0	1.2
Mid-Atlantic	0.9	0.6	0.9	1.3	2.3	1.1
North Central	1.7	0.8	2.5	1.8	4.5	1.1
East North Central	1.1	0.7	2.4	2.1	4.2	1.3
West North Central	3.0	1.9	2.9	3.7	5.3	2.3
South	3.4	0.9	4.3	2.2	7.6	1.3
South Atlantic	2.3	1.0	4.0	2.9	7.2	1.8
East South Central	5.5	2.9	8.7	8.1	10.8	3.2
West South Central	4.2	1.7	2.7	3.1	6.0	2.0
West	1.9	0.8	4.9	2.7	4.9	1.4
Mountain	3.5	2.1	7.2	5.8	7.8	3.5
Pacific	1.4	0.8	3.8	2.9	3.9	1.5

use. As noted previously, use of snuff and chewing tobacco among females is confined almost entirely to the South, and, in keeping with this, the age gradient was most pronounced in the South Atlantic and East South Central divisions.

Among males, the younger age groups typically reported higher rates of using snuff than did other age groups. This raises the question of whether this pattern reflects a recent development, or whether it has been in existence for many years. In particular, if the higher rates of snuff use in the younger adult age groups is a recent phenomenon, then it would document the widespread adoption of snuff among the demographic subgroup targeted by SLT advertising practices in the 1970s and early 1980s (i.e., young adult males). In the 1986 Surgeon General's Report, rates of SLT use obtained from the 1985 CPS were compared with the corresponding rates obtained from the 1970 Na-

tional Health Interview Survey (3). Both surveys 1) adopted reasonably similar survey methodologies, 2) contained large sample sizes (114,000 and 77,000, respectively), and 3) included approximately the same proportion of proxy responses (45%). As shown in table 9, a substantial increase in use of snuff was evident among males 16-29 years of age, with nearly a tenfold increase in use of snuff among males 16-19 years of age. A similar, though less pronounced, pattern was found for males who chewed tobacco.

SIGNIFICANCE OF STATE LEVEL ESTIMATES

The CPS exists as the only survey of the United States population designed to provide national and individual state level estimates of SLT use for all 50 states and the District of Columbia. The results reported herein afford a unique opportunity for state health administrators, researchers, and public health officials to compare SLT use patterns both across and between individual states and regions. Such information will allow state health agencies to plan more effective control efforts in those states where rates are high. The CPS also affords epidemiologists a tool to examine morbidity and mortality patterns among those states with varying levels of tobacco use rates. Economists can examine these data and determine how patterns in use are affected by differences in tax rates among those states or regions where such taxes are applied. If future data collections by researchers using the CPS are conducted, 1985 results could be compared over time with new estimates as a means of assessing policy issues for control of tobacco use for individual states.

DISCUSSION

At the turn of the century, the major form of tobacco consumed in the United States was SLT (4). Of the approximately 7 pounds of tobacco consumed per adult in 1900, 4.1 were in the form of chewing tobacco. The remaining categories of per capita tobacco consumption were 1.63 pounds of pipe tobacco and 0.32 pound of snuff. Total cigar and cigarette consumption accounted for less than

TABLE 7.—Percent current users of snuff by age, region, and division: ≥ 16 -yr-old males

Area	Age ranges (yr) and CI													
	16-19	CI	20-29	CI	30-39	CI	40-49	CI	50-59	CI	60-69	CI	70+	CI
United States	2.9	0.6	2.7	0.3	1.8	0.3	1.5	0.3	1.2	0.3	1.1	0.3	1.9	0.5
Northeast	1.9	1.0	1.2	0.5	1.2	0.5	0.8	0.5	0.9	0.6	0.2	0.3	0.8	0.6
New England	0.5	1.0	0.8	0.8	0.5	0.6	0.1	0.3	0.3	0.7	0.2	0.5	0.3	0.8
Mid-Atlantic	2.3	1.2	1.4	0.6	1.4	0.6	1.0	0.6	1.1	0.7	0.2	0.3	1.0	0.8
North Central	2.6	1.0	2.3	0.6	1.7	0.5	2.2	0.7	1.9	0.7	1.8	0.8	2.7	1.1
East North Central	2.5	1.2	2.2	0.7	1.2	0.5	1.6	0.8	1.3	0.7	1.7	0.9	2.4	1.3
West North Central	2.8	2.0	2.5	1.2	3.0	1.3	3.5	1.7	3.6	1.9	2.1	1.5	3.3	2.1
South	4.7	1.2	4.5	0.7	2.5	0.6	2.0	0.6	0.8	0.4	0.9	0.5	2.2	0.9
South Atlantic	3.9	1.6	2.8	0.8	1.7	0.7	1.3	0.7	0.6	0.5	0.8	0.6	1.6	1.0
East South Central	4.3	2.6	5.5	1.8	1.8	1.1	2.1	1.5	0.8	1.0	0.5	0.8	2.4	2.0
West South Central	6.2	2.5	6.4	1.4	4.0	1.2	3.0	1.3	1.0	0.9	1.3	1.1	3.3	2.0
West	0.9	0.7	1.8	0.6	1.2	0.5	0.8	0.5	1.2	0.7	1.8	0.9	1.6	1.0
Mountain	2.2	2.1	3.4	1.5	1.9	1.2	1.6	1.3	1.8	1.6	2.8	2.2	2.2	2.3
Pacific	0.4	0.6	1.2	0.6	1.0	0.5	0.5	0.5	1.0	0.7	1.5	1.0	1.5	1.1

TABLE 8.—Percent current users of chewing tobacco by age, region, and division: ≥ 16 -yr-old males

Area	Age ranges (yr) and CI													
	16-19	CI	20-29	CI	30-39	CI	40-49	CI	50-59	CI	60-69	CI	70+	CI
United States	3.0	0.6	4.2	0.4	3.7	0.4	3.3	0.4	3.9	0.5	4.2	0.6	4.9	0.7
Northeast	0.7	0.6	1.6	0.6	1.7	0.6	1.3	0.6	0.6	0.4	1.2	0.7	2.7	1.1
New England	1.5	1.7	1.0	0.9	0.7	0.7	0.6	0.8	0.3	0.7	0.8	1.1	0.9	1.4
Mid-Atlantic	0.4	0.5	1.8	0.7	2.0	0.8	1.5	0.8	0.7	0.6	1.3	0.8	3.2	1.4
North Central	3.1	1.1	4.0	0.8	3.6	0.8	3.0	0.9	3.0	0.9	2.8	0.9	3.6	1.3
East North Central	2.6	1.2	3.0	0.8	3.1	0.9	2.5	0.9	3.1	1.1	2.7	1.1	2.8	1.4
West North Central	4.4	2.5	6.7	1.9	4.6	1.6	4.1	1.9	2.7	1.7	3.1	1.8	5.2	2.6
South	4.1	1.1	4.8	0.7	5.6	0.8	5.5	1.0	7.6	1.3	8.0	1.4	8.9	1.7
South Atlantic	3.3	1.4	4.6	1.0	4.8	1.1	4.6	1.3	6.9	1.7	6.6	1.7	6.1	1.9
East South Central	7.3	3.4	7.0	2.1	7.9	2.3	8.7	2.9	11.7	3.6	12.3	3.9	15.5	4.8
West South Central	3.3	1.8	3.8	1.1	5.5	1.4	5.3	1.7	6.2	2.1	8.0	2.5	9.6	3.4
West	3.4	1.4	5.9	1.0	2.7	0.7	2.2	0.8	2.3	0.9	2.6	1.1	1.8	1.0
Mountain	2.8	2.4	11.1	2.7	4.2	1.8	3.1	1.9	3.4	2.2	2.3	2.0	4.2	3.1
Pacific	3.6	1.7	3.9	1.0	2.2	0.8	1.8	0.9	1.8	1.0	2.7	1.3	1.1	1.0

a pound of tobacco per capita annually. The first blended cigarette was introduced in the United States in 1913. Encouraged by heavy advertising and promotion by manufacturers, cigarette smoking had become the predominate form of tobacco consumption by the end of the First World War, a pattern which is still evident today.

Per capita consumption of cigarettes peaked in 1963, the year immediately prior to the release of the original Surgeon General's Report on smoking in January 1964 (*1*). As cigarette smoking became increasingly popular in the decades prior to the 1960s, use of other forms of tobacco, including SLT products, declined, both in the proportion of the population as well as the total pounds of tobacco consumed annually in the United States. In the 1970s, however, SLT manufacturers began to advertise and promote these products aggressively, including new product lines of moist snuff. These products were increasingly promoted on television and other broadcast media (use of these media was banned by Congress for cigarettes and small cigars in the early 1970s). The packages did not contain health warnings, and much of the advertising was targeted toward adolescents and young adult males by prominent sports and entertainment figures.

Unlike cigarette smoking, which still enjoys a much broader social appeal and acceptance nationally, use of SLT

is largely confined to much narrower segments of the population. According to estimates derived from the 1985 CPS, users of these products are primarily males, especially white males, who reside in the southern region of the country. For example, of all users of chewing tobacco in the United States, 90% are male, and of these, 90% are white and 50% reside in the South. A similar pattern is seen among snuff users; nearly 80% are male, of whom 92% are white and more than 50% live in the South. In addition, it should be noted that SLT use is two to three times more prevalent among blue- than white-collar workers.

Also noteworthy is that among males, reported use of snuff in 1985 was highest in the young adults. As reported earlier in table 9, this was not always true. In 1970, the youngest adult age group actually reported the lowest rate of snuff use, with a perfect linear age gradient leading to higher rates of use in the older age groups. However by 1985, this positive age gradient had been replaced by a striking inverse age gradient, highlighted by nearly a tenfold increase in reported use of snuff in teenage boys (16-19 yr). A similar (although less pronounced) 15-year trend was also evident for chewing tobacco, with teenage boys reporting over a twofold increase in use.

Extrapolation of these trends to the total population in the United States indicates an aggregate increase of more than a million new SLT users in 1985 compared with 1970. In contrast, the total number of cigarette smokers between 1970 and 1985 has remained virtually unchanged, despite large increases in the total population base. What impact these additional million or more tobacco users will have on national and regional cancer incidence and death rates will not become fully evident until after the turn of the century.

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TABLE 9.—Prevalence of male SLT use by age, 1970 and 1985^a

Age, yr	Snuff		Chewing tobacco	
	1970	1985	1970	1985
16-19 ^b	0.3	2.9	1.2	3.0
20-29	0.6	2.7	1.9	4.2
30-39	0.7	1.8	2.8	3.7
40-49	1.2	1.5	3.0	3.3
≥ 50	2.7	1.4	6.5	4.2

^a Sources of data were the 1970 National Health Interview Survey and the 1985 CPS.

^b For 1970, this age group was composed of 17- to 19-yr olds.

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Smokeless Tobacco Use in the United States: The Adult Use of Tobacco Surveys

Thomas E. Novotny, John P. Pierce, Michael C. Fiore, and Ronald M. Davis¹

ABSTRACT—Prevalence of smokeless tobacco use is reported for adults aged 21 years and older in the Adult Use of Tobacco Surveys, 1964–1986. Data from the 1986 survey on prevalence, beliefs, ages of initiation, and demographic correlates of use by males aged 17 years and older are also reported. The prevalence of smokeless tobacco use declined slightly among persons aged 21 and older between 1966 and 1986. However, 5.2% of the males aged 17 and older used smokeless tobacco in 1986, and prevalence was highest among those 17 to 19 years old (8.2%). The median age of initiation for both products was 19 years. Smokeless tobacco use was most common among white men who were 1) living in the southeastern United States, 2) unemployed, and 3) in blue-collar or service/labor employment. Most users (77.4%) and nonusers (83.4%) believe that smokeless tobacco is a health hazard. Many current users (39.1%) had attempted to quit. Some current (6.4%) and former smokers (7.0%) have used smokeless tobacco as an aid to smoking cessation. National survey data such as these permit the identification of high-risk groups, so that interventions against smokeless tobacco use may be specifically targeted.—NCI Monogr 8:25–28, 1989.

In the United States, SLT has reemerged as a public health problem (1, 2). National surveys have identified young white males as the group at highest risk of using these products and have shown a higher prevalence among persons living in the southern and north central regions of the United States (3–5). In the longitudinal Bogalusa Heart Study, 8- to 17-year-old white males reported a large increase in SLT use between 1976 and 1981, including an eightfold increase in the use of snuff (6). American Indians and Alaskan Natives also have a high prevalence of SLT use (7, 8). Most disturbing is the national trend toward higher use among men who are less than 21 years old. Between 1970 and 1985, snuff and chewing tobacco use increased tenfold and more than twofold, respectively, among males aged 17 to 19 years. Smaller increases were observed among the middle-aged groups, and a decrease in the use of both products was noted for older men aged 50 and above (1).

The National Institutes of Health Consensus Development Conference Statement on the Health Implications of Smokeless Tobacco Use called for additional studies of SLT use based on national probability sample data (9). In 1986,

the Office on Smoking and Health conducted the AUTS on a nationally representative sample of the resident adult population in the United States (10). Questions regarding SLT use were included in this survey, as well as in earlier AUTS conducted in 1964, 1966, 1970, and 1975 (11–13).

In this article, we compare data on its use among persons aged 21 or older from the AUTS. We also report a more detailed analysis of the correlates of SLT use, including attitudes and beliefs, from the 1986 AUTS for males aged 17 and older.

METHODS

Prevalence data for the use of chewing tobacco and snuff separately were collected by the National Clearinghouse for Smoking and Health (now the Office on Smoking and Health) through the AUTS for 1964, 1966, 1970, 1975, and 1986 (10–13). In each survey year, smokers were oversampled, and the final data were weighted to adjust for this oversampling. For the 1964, 1966, 1970, and 1975 surveys, data were collected from the civilian, noninstitutionalized United States population aged 21 years and older. In 1986, data were collected from persons aged 17 years and older. The respondents were selected as a national probability sample in each year. The 1970 and 1975 surveys were telephone based, but the 1964 and 1966 surveys were conducted by personal interview. The prevalence of current SLT use among persons aged 21 and older was stratified by product and sex and was reported for each survey year.

In the 1986 AUTS, data were collected from a sample [drawn according to the Waksberg-Mitofsky random digit dialing technique (14)] of 13,031 persons (6,377 men and 6,654 women) aged 17 years and older. These data were weighted to the United States population, based on the 1986 Current Population Survey of the Bureau of the Census (15). This procedure controlled for the race, sex, education, and regional distribution of the population in the United States. The 1986 survey asked more detailed questions regarding the use of SLT. Because so few women surveyed in 1986 had ever used such products (0.5%), we restricted the remainder of our analysis to data from male respondents. We report the prevalences of use of any, either, or both SLT products for men aged 17 years and older. We also calculated the prevalence of ever and current use of any SLT product stratified by demographic categories, including age, race, region, education, poverty level [as defined by the Census Bureau criteria (16)], employment, and household income. These variables were included in a multivariate model using the CATMOD procedure in the Statistical Analysis System or SAS (17); the final model includes

ABBREVIATIONS: SLT = smokeless tobacco; AUTS = Adult Use of Tobacco Survey(s).

¹Office on Smoking and Health, Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control, Department of Health and Human Services, Park Building, Room 1-10, 5600 Fishers Lane, Rockville, Maryland 20857. Address reprint requests to Thomas E. Novotny, M.D.

only those variables found to be significant in predicting the outcome of current SLT use. Ninety-five percent confidence limits about the odds ratios for each parameter included in the final model are reported.

Respondents were also asked if they had attempted to quit using it, whether they experienced difficulty in quitting, and when had they begun to use SLT products regularly (initiation). We reported the age group at initiation and median ages at initiation by the product used as well as by product and birth cohort (before 1950 and 1950–1969). In addition, both users and nonusers were asked about their beliefs regarding the harmfulness of SLT.

To determine if SLT is used as an alternative to smoking, interviewers asked current and former cigarette smokers whether they had used it as an aid to quitting smoking; this percentage and the percentage of current and former smokers using formal cessation programs are reported.

RESULTS

The prevalence of snuff and chewing tobacco use among men and women aged 21 and older from 1964 to 1986 has declined slightly (table 1). Among adults aged 21 or older in 1986, the weighted prevalence of snuff use was 2.2% for men and 0.5% for women, and for chewing tobacco it was 3.1% for men and 0.1% for women.

For 1986, overall prevalence of “ever use” and “current use” of SLT among males aged 17 and older is shown in table 2. More than 12% of the male respondents had ever used SLT products; chewing tobacco appears slightly more commonly used than snuff. Few (0.5%) men use both products simultaneously.

For men, the prevalence of ever use and current use of any SLT product, stratified by selected sociodemographic variables, was highest among younger white men who 1) were living in the Southeast, 2) had lower levels of education, 3) had lower income, 4) were below the poverty level, and 5) were unemployed (table 3).

All sociodemographic parameters in table 3 were entered in a multivariate model for which current use was the outcome variable and were then eliminated if they did not contribute significantly to predicting current use of SLT. The final model included race, occupation, and region. In this model, white men were more than twice as likely as black men to use SLT; men employed in blue-collar or service/laborer jobs or who were unemployed were three times more likely than white-collar workers to use it; and men in the Southeast and West were more likely than men in other regions to use SLT (table 4).

TABLE 1.—Prevalence (%) of SLT use: 1964–1986, AUTS^a

Year	Men		Women	
	Snuff	Chewing tobacco	Snuff	Chewing tobacco
1964	2.0	5.1	2.0	0.5
1966	3.1	7.1	2.1	0.4
1970	2.9	5.6	1.4	0.6
1975	2.5	4.9	1.3	0.6
1986	2.2	3.1	0.5	0.1

^a Adults surveyed were aged 21 yr and older.

TABLE 2.—Prevalence (%) of ever use and current use of SLT: males aged 17 and older, 1986

Product used	Ever use	Current use
Any SLT	12.6	5.2
Snuff	5.8	2.4
Chewing tobacco	9.9	3.3
Both ^a	3.1	0.5

^a Percentages were obtained by subtraction of any SLT from the sum of snuff and chewing tobacco.

Two-thirds of the men who ever used SLT began use before they were 21, and more than one-third began before they were 16 (table 5). Because the ranges for age of initiation of SLT use are wide (8 to 59 yr for snuff and 6 to 75 yr for chewing tobacco) and the distribution is skewed toward the younger years, the median age of initiation was used as the measure of central tendency. The median age of SLT initiation for both products is 19. Categorized by birth cohort, men born from 1950 through 1969 had a lower median age of initiation than those born before 1950 for both snuff (18 vs. 25) and chewing tobacco (18 vs. 20) as shown in table 6.

TABLE 3.—Prevalence (%) of ever use and current use of any SLT by sociodemographic categories, males aged 17 and older, 1986

Category	Ever use	Current use	Population	Sample size
Age group, yr				
17–19	12.3	8.2	5,365,000	299
20–29	11.4	5.9	20,345,000	1,208
30–39	7.3	4.1	18,593,000	1,495
40–49	9.7	5.0	12,778,343	1,128
>50	11.5	4.8	26,844,167	2,247
Race				
White	11.1	5.6	72,073,331	5,703
Black	6.6	3.0	8,588,942	465
Other	7.7	2.9	3,263,237	209
Geographic area				
Southeast	14.5	7.5	29,231,720	2,110
West	9.6	4.5	17,147,702	1,290
Midwest	9.5	4.3	19,915,891	1,570
Northeast	5.5	3.0	17,630,198	1,407
Completed years of school				
≤11	14.6	7.3	22,222,266	1,258
12	11.1	5.6	28,887,445	2,240
13–15	9.1	3.8	15,877,148	1,448
≥16	4.8	2.9	16,938,651	1,431
Poverty level				
Below	16.1	8.5	6,582,762	390
Above	9.9	4.9	65,039,406	5,115
Employment				
Unemployed	13.0	8.3	3,270,903	173
Service/laborer	12.3	6.4	12,100,216	794
Blue collar	7.0	3.6	31,645,988	2,367
White collar	2.3	1.0	33,128,857	2,754
Annual household income				
<\$10,000	16.1	8.6	6,124,778	416
\$10,000–29,999	4.7	2.2	32,744,319	2,439
≥\$30,000	3.0	1.6	32,753,069	2,650

TABLE 4.—Significant sociodemographic correlates of any current SLT use, males aged 17 and older, 1986

Parameter	Odds ratio	95% confidence limits
Region		
Southeast	3.0	1.8, 4.8
West	1.9	1.1, 3.3
Midwest	1.4	0.8, 2.5
Northeast	Referent	
Race		
White	2.4	1.3, 4.3
Black	Referent	
Employment		
Unemployed	3.8	1.9, 7.6
Blue collar	3.0	2.1, 4.3
Service/laborer	2.9	1.8, 4.6
White collar	Referent	

Among current users, 77.4% believe that SLT use is a health hazard; among nonusers, 83.4% believe its use is hazardous. Among current users, 39.1% had attempted to quit, and of these, 46.7% reported experiencing difficulty in doing so.

Among current and former smokers, 6.4% and 7.0%, respectively, used SLT to help them quit smoking. In contrast, 2.4% of current and 1.7% of former smokers used organized programs to help them quit smoking.

DISCUSSION

The AUTS indicate overall that the use of SLT products among persons aged 21 and older declined slightly between 1964 and 1986. However, the production of these products in the United States increased 40% between 1970 and 1986, from 95.2 million to 132.8 million pounds (18). The discrepancy between prevalence and production data is only partly explained by the increase in population. Between 1970 and 1986, the population over the age of 14 years (the potential users) grew from 151 to 193 million, an increase of almost 28% (19, 20). The increase in production above what might be expected from the growth in population has three possible explanations: Either the number of persons under the age of 21 who use SLT has increased, or users have increased their use, or both. Age-stratified prevalence of snuff and chewing tobacco use from the 1985 Current Population Survey has been compared with similar data from the 1970 National Interview Survey (21). For males aged 17 to 19 years, the prevalence of snuff and chewing tobacco use increased from 0.3% to 2.9% and from 1.2% to 3.0%, respectively; prevalence among men 20 to 49 years old increased less dramatically and declined for men aged 50 and older. This behavior change occurred despite the

TABLE 5.—Reported age and median age of initiation of male SLT users, aged 17 yr and older, 1986

Product	Age group at initiation, yr ^a				Median
	<16	16-18	19-20	21+	
Any SLT	37.1	7.8	21.4	33.8	19
Snuff	35.5	8.6	23.0	32.8	19
Chewing tobacco	36.6	6.7	20.3	36.3	19

^a Values represent percentages of males reporting.

TABLE 6.—Median age of initiation of male SLT users aged 17 and older, by birth cohort, 1986

Product	Birth cohort	
	Before 1950	1950-1969
Any SLT	21	17
Snuff	25	18
Chewing tobacco	20	18

fact that most men were well aware of the hazards of using SLT in 1986.

Because of the relatively small proportion of users among respondents in the nationally based 1986 AUTS, prevalence estimates among subgroups may be unstable. Nevertheless, the multivariate model shows that SLT use among men, like cigarette smoking, is a greater problem for those who are unemployed, employed in blue-collar or service/laborer jobs (22), or live in the South (23). In contrast to cigarette smoking (22), SLT use is more common among whites than among blacks.

Most importantly, nearly two-thirds of the current users of snuff and chewing tobacco began using them before they were 21 years old. Our data also suggest that younger men (born in 1950 or later) began to use SLT earlier in life than did men in the older birth cohorts. However, because 50% of the men in our sample began using it after they reached age 19, this cohort effect may be biased, insofar as some nonusers in the most recent birth cohort will begin to use SLT after their teenage years and therefore would not be detected in this survey.

Among high school seniors, the prevalence of regular cigarette smoking has consistently been higher for women than for men (21); some of this difference in smoking prevalence between genders has undoubtedly been offset by the dramatically higher prevalence in recent years of SLT use among young men (21).

As cigarette smoking becomes less socially acceptable in the United States, adult smokers may try to quit smoking by using alternative nicotine delivery systems such as nicotine polacrilex gum or snuff and chewing tobacco. They may also use SLT products in schools, workplaces, or other environments that have restrictions against smoking. Several brands of SLT have been advertised as acceptable substitutes when smoking is not permitted. Policies regulating exposure to environmental tobacco smoke at worksites and public places are proliferating (24), and a comparison of this situation to the regulatory climate at the turn of the century proves interesting. At that time, tobacco spitting was identified as an environmental health risk. As a result, laws regulating public spitting were established, and the tobacco industry developed a "cleaner" product: the mass-produced cigarette (25). The spittoon disappeared as the ashtray became commonplace. Now that environmental tobacco smoke has been identified as a health hazard, SLT use has reemerged among young adults, perhaps partly because of restrictions against smoking. The reemergence of use among children was also highly correlated with the increase in advertising for these products (26).

Nicotine is an addictive drug, and all tobacco products contain substantial amounts of nicotine. Although the deliv-

ered biologic dose cannot be accurately predicted from the nicotine content of the product, the resulting blood levels of nicotine produced by SLT use are similar in magnitude to those produced by smoking cigarettes (21). Therefore, it is not surprising that almost 50% of the men in our sample who had attempted to quit using SLT reported difficulty in doing so. We did not ascertain the percentage of former users who went on to smoke cigarettes. Additional longitudinal research is needed before the natural history of SLT use relative to both smoking and switching products can be described.

Young users of snuff and chewing tobacco may switch to cigarette smoking to satisfy their nicotine addiction when they reach adulthood. Although among males use of SLT may be perceived as more socially acceptable by teenagers, it also may be perceived as less socially acceptable by adults. This perception may prompt young adults to change to cigarette smoking and thus increase their health risk. We have shown that both current and former smokers use SLT as an aid to smoking cessation more frequently than they use organized cessation programs. However, we were unable to ascertain the comparative success of these techniques with our survey.

We have learned a great deal about cigarette smoking as a national public health problem. Although the prevalence of SLT use is far less than that of smoking in the United States, i.e., approximately 30% (10), we must apply the same public health strategies for prevention and cessation to this health risk behavior that we do to smoking. Several governmental efforts to decrease the use of SLT have recently been enacted, including health warnings on product packages and advertisements, banning SLT advertising in the broadcast media (27), and imposing a small federal excise tax. Although the adverse health effects of SLT have not become widespread in the United States, they have been carefully documented (1). The public health community and policy makers now have a unique opportunity to prevent the potential impact of these health problems; to accomplish this end, their targeted efforts to prevent SLT use, especially among young men, are needed.

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Epidemiology of Smokeless Tobacco Use: A National Study¹

Beatrice A. Rouse^{2, 3}

ABSTRACT—The prevalence and patterns of smokeless tobacco use and its correlates were assessed in the National Institute on Drug Abuse National Household Survey of residents 12 years of age and older. Overall, 11% of the general population have “ever tried” chewing tobacco, snuff, or other smokeless tobacco. Of these, 5% were former users and 3% used smokeless tobacco almost daily in the past year. Rates of its use differed significantly by sex, age group, race, region, and metropolitan area size. Although females were far less likely to try it, those who did were as likely as males to be daily users. Smokeless tobacco users were also more likely to use alcohol, cigarettes, and marijuana. In general, those who used smokeless tobacco almost daily were more likely to report poor health and hospitalization for illness or injury in the past year, even when other substance use was controlled. Smokeless tobacco users also were more likely to report symptoms of depression. Finally, some substituted smokeless tobacco for cigarettes, but youths (12–17 yr old) were more likely than older tobacco users to use both forms of tobacco regularly.—NCI Monogr 8:29–33, 1989.

Tobacco chewing first became popular in the early nineteenth century when it became known as “The American Habit” while other parts of the world mainly used dry snuff (1). Although the first American tobacco advertisement was published in 1789 by Lorillard, most tobacco users sniffed or chewed tobacco until the first quarter of the twentieth century. Then smoking tobacco increased due to the mass production, advertising, and reduced cost of cigarettes. As a result of this technology, as well as the increased health concerns regarding the spread of airborne diseases from tobacco spitting, SLT use decreased. Smoking cigarettes has remained the most popular form of tobacco use. In the latter part of the twentieth century, however, the public has become increasingly aware of health risks associated with cigarette smoking and its associated passive effects and with tobacco’s addictive properties (2). Now SLT is being considered by some as an alternative to cigarettes. Comparable nicotine levels are achieved with either form of

tobacco (3). Therefore, medical concerns are being raised regarding carcinogenesis, nicotine dependence or addiction, dental problems, and other health effects associated with the use of SLT (3, 4).

In the 1970s, regular SLT use in the United States was low and remained fairly stable. Use was generally higher among males, nonsmokers, and residents in the southern states; moreover, chewing tobacco was used more than snuff (5–7). The national surveys of adults aged 21 years and older conducted by the Office on Smoking and Health found that rates of lifetime SLT use increased since 1964, peaked in 1970, and remained relatively stable in 1975. In the peak year of 1970, among males, 25% had “ever tried” chewing tobacco and 7% had ever tried snuff; among females, 2% had ever tried chewing tobacco and 3% had ever tried snuff. Six percent of the males and 1% of the females chewed tobacco, and 5% of the males and 1% of the females used snuff currently. National rates of SLT use among youth, however, were unknown for the 1970s.

In the 1980s, small-scale studies in various regions have produced estimates of SLT use in adolescents that have ranged from 5% to 36% (8–18). Moreover, such studies suggest that the lifetime and current prevalences of its use by youth have increased in the last decade. For example, longitudinal data from the Bogalusa (Louisiana) Heart Study indicated a doubling in tobacco chewing and a tripling in snuff dipping between 1976 and 1981 among 8- to 17-year-old white males. In 1981, the highest rate of chewing tobacco was 43% in 14- to 15-year-olds and the highest rate of snuff dipping was 32% in 12- to 13-year-olds (12).

This report presents data from a recent national study of the general population. The prevalence, patterns, and correlates of SLT use were examined, so that how generalized and widespread this form of tobacco use has become could be determined. The self-perceived health status of the respondents was also examined.

METHODS

Data on SLT use were collected as part of the National Household Survey on Drug Abuse. This survey is conducted periodically by the National Institute on Drug Abuse to gather data on the prevalence, correlates, and trends of drug abuse in a representative sample of the household population 12 years of age and older in the coterminous United States. In 1985, a national stratified multistage probability sample of household residents was drawn that included an oversampling of blacks and Hispanics and of the younger age groups. Only one eligible resident was randomly drawn from each household. Sampling weights and the appropriate statistical adjustments were applied to obtain the preva-

ABBREVIATION: SLT = smokeless tobacco.

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²Epidemiology Research Branch, Division of Epidemiology and Statistical Analysis, National Institute on Drug Abuse, Department of Health and Human Services, 5600 Fishers Lane, Room 11A-55, Rockville, Maryland 20857.

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lence rates and population estimates of drug use. Group differences were tested by chi-square analyses appropriately adjusted for the design effect of the complex sampling. Statistical levels of .05 or less were considered significant. Regional classifications were based on the Bureau of Census geographical divisions.

Data were collected by trained interviewers who combined personal interview procedures with a self-administered questionnaire. The interviewers recorded the information about the respondents' tobacco use, health, and sociodemographic characteristics. For the questions regarding illicit drug use, the respondents recorded their answers on self-administered questionnaires during the interview to maintain confidentiality and anonymity. Data were collected between June and December 1985. The overall response rate was 84% and the sample size was 8,038. The 1985 National Household Survey on Drug Abuse was the eighth in the series but the first to gather data on SLT. Respondents were asked: "On the average, in the past 12 months, how often, if ever, have you used chewing tobacco or snuff or other smokeless tobacco?"

RESULTS

Prevalence and Patterns of Population Use

An estimated 11.1% of the household population aged 12 years and older used chewing tobacco, snuff, or other SLT at least once in their lifetime. When applied to current population census figures (19), this lifetime prevalence rate produced a point prevalence estimate of 21.2 million household residents who have ever tried SLT. Of the estimated 12.3 million who used it at least once in the past year, 5.5 million did so almost daily. The lifetime prevalence rate for any SLT use for adults aged 21 years and older was 19% for males and 3% for females; for 12- to 20-year-olds, it was 28% for males and 3% for females. Overall, 2.9% in the household population 12 years old and older used it almost daily, 3.6% used it less often in the past year, 4.7% were former users, and 88.8% never chewed or dipped.

Significant differences were found in rates of SLT use by sex, race and/or ethnicity, and age group (table 1). Any lifetime use was relatively rare among females (3%) compared with males (20%). In the total sample, lifetime

prevalence was higher among non-Hispanic whites (12%) than blacks (9%) or Hispanics (5%). Among males, the younger age groups and non-Hispanic whites had higher lifetime and past-year use rates of SLT. Among blacks, the highest rates for both males and females were among the older adults. Furthermore, older black females who had ever tried SLT were more likely to be current daily users. Among black males aged 55 years and older, 32% had used SLT in their lifetime and 9% were currently using it daily. Among black females in the same age range, 19% had used it in their lifetime and 12% were currently daily users.

Among males who had ever tried SLT, 60% used it in the past year; among females who had tried it, 42% used it in the past year. The females who were users in the past year, however, were older, black, and more likely to use SLT almost daily. Although few females had ever tried it, those who did use it in their lifetime were as likely as the males to have used it almost daily in the past year (26%).

Overall, among males who used SLT in the past year, 43% used it almost daily, 8% on 1 to 2 days per week, 29% on about 3 to 51 days in the past year, and 20% on 1 to 2 days. The frequency of use in the past year among male users is shown by age group and race or ethnicity in table 2. Most (93%) of the older blacks who used it in the past year chewed or dipped almost daily.

Regional differences in lifetime and past-year prevalence rates are shown by sex and age in table 3. Prevalence rates were generally lower in the Northeast but comparable in the other regions. Furthermore, over 50% of those who had ever tried SLT were using it in the last year in all areas. Given the low rate of use among females, the large proportion of lifetime and past-year users among the 12- to 17-year-olds in the North Central region is especially noteworthy. Further examination of these users indicated that none lived in large metropolitan areas, and all the daily users were in rural areas or small cities.

Indeed, size of metropolitan area was significantly related to SLT use for males and females and all age groups. Lifetime, past-year, and daily use were highest in non-metropolitan areas. For example, among the total sample of males, 15% of those in large (population more than 250,000) and 17% of those in small metropolitan areas (50,000-250,000), and 27% of those in rural areas have used SLT at least once in their lifetime. Furthermore, the rate of current daily use among males in the nonmetropolitan areas was over four times that in the large metropolitan areas (9% vs. 2%).

TABLE 1.—Percentage of household residents 12 yr of age using SLT ever (E) and past year (P) by race and/or ethnicity, sex, and age group

Sex	Age group, yr	Whites		Hispanics		Blacks		Total	
		E	P	E	P	E	P	E	P
Males	12-17	30	25	8	6	8	4	25	20
	18-25	38	25	8	4	9	5	32	21
	26-34	20	11	4	3	9	7	18	10
	35+	17	9	9	2	18	5	14	8
	Total	22	14	8	3	13	5	20	12
Females	12-17	3	2	1	1	3	1	3	2
	18-25	3	1	3	1	2	2	3	1
	26-34	3	2	1	^a	3	1	3	2
	35+	2	^a	2	1	11	6	3	1
	Total	2	1	2	1	7	3	3	1

^a Use was <0.5%.

TABLE 2.—Percentage distribution of frequency of SLT use among past-year male users for whites (W), Hispanics (H), and blacks (B) by age group

Frequency	Age group, yr											
	12-17			18-25			26-34			35+		
	W	H	B	W	H	B	W	H	B	W	H	B
Most days/wk	23	^a	^a	48	40	31	49	39	32	49	^a	93
1-2 days/wk	7	8	8	6	15	5	12	^a	19	7	^a	^a
3-51 days/yr	41	13	24	31	9	18	19	41	26	27	40	7
1-2 days/yr	29	79	67	15	35	46	20	19	24	18	60	^a

^a See footnote, table 1.

TABLE 3.—Percentage of household population using SLT ever (E) and past year (P) by region, sex, and age group

Sex	Age group, yr	North-east		South		West		North Central	
		E	P	E	P	E	P	E	P
Males	12-17	13	11	30	24	28	25	29	22
	18-25	24	18	33	24	35	19	36	21
	26-34	8	5	18	13	20	12	21	8
	35+	8	3	22	12	15	6	18	9
	Total	11	7	24	16	21	12	23	13
Females	12-17	1	^a	2	1	3	1	8	4
	18-25	1	1	1	^a	5	3	4	1
	26-34	3	1	4	3	3	2	1	1
	35+	3	1	2	1	2	^a	3	1
	Total	2	1	3	2	3	1	3	1

^a See footnote, table 1.

The relationship between educational status and SLT use was examined in the age group of highest use, i.e., 12-25 years. Use for youth who were still in school is shown by sex and grade in table 4. Daily use was highest among older male students and ranged from less than 0.5% for 6th grade to 12% for the 12th-grade males. Among females, rates of daily use were consistently low across all grade levels. Young adults were classified by highest level of education attained: college students, high school graduates, or high school dropouts. For both sexes, lifetime prevalence and past-year use were lowest for college students. Among males, daily use was highest among school dropouts (13%) and lowest among college students (6%).

Cigarette and Other Substance Use

Cigarette smokers at all ages were more likely to have tried SLT, and current smokers were also more likely to use it. Among the 12- to 17-year-old males, 14% of those who never smoked cigarettes, 32% of the former smokers, and 41% of those who smoked in the last year have tried SLT in their lifetime. Among females of the same age group, 1%

of those who never smoked, 5% of the former smokers, and 7% of those who smoked in the last year have tried SLT in their lifetime. Younger smokers were more likely than older smokers to use cigarettes and SLT regularly. Among the 12- to 17-year-old males, 4% of those who smoked no cigarettes in the past month, 8% of those who smoked about one-half pack, and 7% of those who smoked at least a pack daily either chewed tobacco or dipped snuff almost daily. In contrast, among males aged 35 years and older, 4% of the nonsmokers, 18% of the half-pack smokers, and less than 1% of the smokers of a pack daily used SLT daily.

Those who smoked cigarettes and drank alcoholic beverages in the past year were the most likely to have ever tried SLT; however, those who only drank were almost as likely to use it. Among males aged 12-17, 30% of those who only drank also used SLT at some time in their life, compared with 11% of those who neither smoked nor drank and 41% of those who did both in the past year. The relationship was the same among older males, but the rates of substance use were lower.

Tobacco chewing and snuff dipping were also associated with recent use of marijuana even in the older age groups. Among males, a comparison by age group of the percentage reporting simultaneous use of SLT and marijuana in the past year is shown by the following data:

Age group, yr	Marijuana status	
	User	Nonuser
12-17	37	15
18-25	23	17
26-34	11	8
35+	16	8

Health in Past Year

Respondents were asked, "Would you describe your health for the past 12 months as excellent, very good, good, fair, or poor?" Those who had ever used SLT were more likely than nonusers to describe their health status for the past 12 months as less than good. In the total sample, 18% of the daily users, 13% of the former users, and 11% of the nonusers reported poor health in the past year. Furthermore, SLT users in general and daily users in particular reported higher rates of hospitalization overnight because of injury or illness in the past 12 months. Among males, 9% of the nonusers and 16% of the daily users and, among females, 9% of the nonusers and 30% of the daily users reported such hospitalization. Rates of hospitalization among youth and young adult daily users compared with nonusers, however, were not significantly different. Rates of hospitalization are shown by SLT use, age group, and sex in table 5. In general, past-year daily users reported poorer health and more hospitalizations even when the use of other substances was controlled. For example, of the males who neither smoked cigarettes nor drank in the past year, 8% of those who also did not use SLT were hospitalized, compared with 13% of the daily SLT users.

As a measure of emotional health, the respondents were asked to indicate how often in the past week they felt var-

TABLE 4.—Percentage of SLT use among students by grade and sex

Sex	Grade	Ever	Almost daily ^a	Less than daily	Not in past year
Males	6	30	^b	21	10
	7	20	^b	14	6
	8	18	4	7	7
	9	29	4	23	2
	10	22	4	12	5
	11	27	5	19	3
	12	36	12	17	7
Females	6	4		^a	4
	7	1		^a	1
	8	1		^a	^a
	9	4		1	3
	10	4		2	2
	11	5	2	1	2
	12	5		3	1

^a Use for female students in grades other than 11 was <0.5%.^b See footnote, table 1.

TABLE 5.—Percentage of household residents hospitalized in past year by SLT use, sex, and age group

Sex	Age group, yr	SLT use				Total
		Never	Almost daily	Less than daily ^a	Not in past year	
Males	12-17	8	7	5	9	8
	18-25	8	5	17	3	9
	26-34	6	22	14	5	7
	35-54	9	15	9	15	9
	55+	11	36	26	20	13
Females	12-17	5	<i>b</i>	9	<i>b</i>	5
	18-25	8	16		<i>b</i>	8
	26-34	11	30		14	11
	35-54	7	70		10	7
	55+	14	34		8	14

^a Use by female residents in age groups other than 12-17 was <0.5%.

^b Use was <0.5%.

ious symptoms of depression. Among males and females, more former SLT users reported feeling depressed often in the past week than either daily users or nonusers. Among the males, those who chewed tobacco or dipped snuff were more likely than nonusers to report that most days everything that they did "was an effort" (24% vs. 12%) and that most days they could not "get going" (10% vs. 3%).

DISCUSSION

Rates of SLT use in the general population were highest among white male 12- to 25-year-olds who were residents of nonmetropolitan areas. This finding is consistent with that of regional and other small-scale studies, which suggests that such use is not a localized phenomenon. Although males are more likely to try SLT, those females who did try it were as likely as males to become daily users. Although the unsightliness of the practice is likely to prevent most persons from using SLT, several factors are currently operating to increase its use: 1) increased public emphasis on a smokefree environment, 2) increased availability of various products, and 3) advertisements featuring prominent sports figures that teach how the product is to be used.

The results from this national study suggest that there are two distinct types of users with differing implications for the health care delivery system. First are the young users. Youths are more likely to experiment with SLT products, but almost 50% of those 18 and older who use it are daily users. Some substitute it for cigarettes, but they tend to use both forms of tobacco. Often their range of substance use is related to rebellious attitudes toward adults and authority and to risk-taking. Public health and civic leaders who conduct SLT prevention- and treatment-related activities targeted to youth and young adults need to take into account their cigarette smoking and illicit substance use and the motivations for such behavior.

The second type is the older cohort who has chewed tobacco, dipped snuff, or used other smokeless products daily for many years. Although there are long-term health implications for the young SLT users, the older ones have more immediate and severe medical needs. These users

include especially those blacks over 55 and a cohort of older white southern women who continue to use SLT and who are more likely to prefer it to cigarettes. Therefore, prevention and intervention programs must focus on the health effects of tobacco, regardless of the form used.

Finally, SLT users in general are at risk for numerous health problems especially given their multiple drug use. Indeed, they are more likely to perceive their health as poor, to report symptoms of depression, and to be hospitalized for illness or injury. As a result, where medical and mental health care is accessible, even the young SLT user is likely to come to the attention of health care professionals. Although such individuals may not have been referred because of their use of it, such contact provides the health professional the opportunity to identify for these individuals and to educate them about the fact that SLT is but a form of tobacco and as such carries many of the same undesirable dependence-producing behaviors and adverse health consequences as cigarettes.

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Use of Smokeless Tobacco by Age, Race, and Gender in Ten Standard Metropolitan Statistical Areas of the Southeast United States¹

Karl E. Bauman, Gary G. Koch, Lynn A. Fisher, and Elizabeth S. Bryan^{2, 3}

ABSTRACT—Most surveys of smokeless tobacco use have been limited to young people, and in the few studies of adults, researchers have not considered age, race, and gender simultaneously, although broad age groups have been used. Data on smokeless tobacco use by race and gender for 5-year age groups up to age 70 and older were compiled from 21,203 households in 10 Standard Metropolitan Statistical Areas of the southeastern United States.—NCI Monogr 8:35–37, 1989.

The harmful effects of SLT (1) and public policy regarding its use (2, 3) have attracted substantial attention. These concerns can be viewed in the context of many studies of SLT use by young people. Boyd and associates (4) presented original findings on the prevalence of use by race, gender, and grade in school for 14 surveys of children and adolescents conducted since 1983, and they cited the studies of adolescents that had been reported earlier. In sharp contrast to this wealth of information for young people is the paucity of data that describes adults according to basic demographic characteristics. The few earlier studies of SLT use by adults, which are described in the report to the Surgeon General (1), did not present results by age, race, and gender simultaneously. Moreover, the studies showing use by age were of broad age groups. Our purpose is to describe the prevalence of SLT use by race and gender for a wide range of ages in 10 SMSA in the southeastern United States.

METHODS

The data reported here are from a field experiment that was conducted for an assessment of the influence of a mass media campaign on adolescent cigarette smoking. The study required area probability samples of households in 10 SMSA in the southeastern United States. As part of the screening procedure to identify eligible adolescent subjects, we asked adult members of 21,267 households to provide information on the race, gender, age, and SLT use of household members.

ABBREVIATIONS: SLT = smokeless tobacco; SMSA = Standard Metropolitan Statistical Area(s).

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²School of Public Health, CB #7400, Rosenau Hall, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599. Address reprint requests to Karl E. Bauman, Ph.D.

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The procedures for selecting the 10 SMSA were as follows: The 81 SMSA in the Southeast were systematically studied with the use of available 1980 Census data. To enhance internal validity for the field experiment, we identified the SMSA that had similar social and economic characteristics. There were 16 such SMSA, and 10 were needed for the research. We chose the 10 by using a table of random numbers and stratification to eliminate proximate SMSA as necessary to prevent overlap in mass media markets. The 10 SMSA are Chattanooga, TN; Columbia, SC; Jackson, MS; Lakeland, FL; Lexington, KY; Macon, GA; Mobile, AL; Montgomery, AL; Roanoke, VA; and Savannah, GA. Averages of selected characteristics for the 10 SMSA, with ranges across SMSA in parentheses, are 322,142 inhabitants (224,341 to 443,536), 29.2 years of age (27.2 to 32.7), 73.9% white (60.1 to 88.2), 15.7% with 4 or more years of education (11.4 to 21.3), and \$18,078 median family income (\$16,512 to \$19,388).

Within each of the 10 SMSA, 1980 Census enumeration districts and block groups were used to form area segments, which contained one or more clusters of household units with an estimated 2.8 persons 12 to 14 years of age per cluster. Approximately 80 clusters were randomly selected in each SMSA, and the 30,561 housing units within the chosen clusters were then visited by field personnel to obtain the information on household members that was necessary to identify adolescent subjects. Field personnel made at least two attempts to obtain the information from a member of the household unit who was 16 years of age or older. If these attempts were unproductive, the staff tried to contact another knowledgeable person, such as a neighbor, to learn whether a person approximately 12 to 14 years of age lived in the house. When information from a nonmember of the household suggested that the household might contain an eligible 12- to 14-year-old subject, our efforts to contact an adult household member continued, whereas if no eligible subject was reported to live in the household, no further attempts were made to screen the household.

Of the 30,561 household units, 2,788 were eliminated from further study because they were not occupied permanent residences. A member of each household provided information for 21,267 of the 27,773 remaining households. Information was unavailable from 6,506 households because members of 43 refused to participate, 647 were not contacted, and, for 5,816, a knowledgeable person (who did not live in the household) indicated that no persons aged 12 to 14 lived in the household. Sixty-four of the 21,267 households with information from a household member were lost to study for unknown reasons, yielding 21,203 for study.

Interviewers contacted the available adult member in

each of the 21,203 households to identify the race, gender, and age of each household member; a total of 55,709 members were identified. The interviewer also asked whether anyone living in the house now used chewing tobacco or snuff. If the answer was yes, the interviewer asked who was the user of chewing tobacco or snuff to identify each user in the household. The 349 household members who were not white or black were omitted from these analyses because there were too few for reliable estimates across age and gender categories, and 852 household members were eliminated because information on gender, race, age, or SLT use was incomplete. Thus a total of 54,508 household members were used in these analyses.

RESULTS

Reported use of SLT by age, race, and gender is shown in table 1. Few in the two youngest age groups (0 to 4 and 5 to 9 yr) were identified as users of SLT, with no more than 0.3% use in any race or gender group for those ages. The remainder of our report deals with persons 10 years of age and older.

The evaluation of trends in use across age was done for each race and gender group by correlation chi-square tests, which were specifically directed at this type of potential association (5). The results for white females, black males, and black females were statistically significant ($P < .01$) and thereby revealed increases in use with age. Among white males, those 15 to 24 years of age were found by regular chi-square tests to be significantly more likely than younger or older males to use SLT ($P < .01$). Also for white males, the age groups of 25 to 29 years and older were not significantly different in use.

Comparisons of use by males and females within each race and age group were based on chi-square tests for 2×2 tables or on Fisher's exact test when expected frequencies for users were small. For whites in each age group, males were more likely than females to use SLT ($P < .01$). There

was no clear gender difference pattern for blacks. Among blacks 15 to 19, 25 to 29, and 65 to 69, males were significantly more likely than females to use SLT; the only other age group with a significant gender difference was for those 70 and older, with females more likely to use it than males ($P < .01$).

Use by whites and blacks within gender and age groups was also compared. For most of these analyses, chi-square tests were applied; for females in the 15- to 39-year age groups, Fisher's exact test was used because of the small expected frequencies of users. Among males for each 5-year age group less than 45 years, whites were more likely to use SLT than were blacks ($P < .01$). White and black males aged 50 to 64 and 70 and older did not differ in use. Of the males 65 to 69 years of age, blacks were more likely than whites to use snuff or chewing tobacco ($P < .01$). Use among white and black females less than 30 years of age was similar. For females 30 years of age and older, blacks were significantly more likely than whites to be users ($P < .01$).

The race, gender, and age groups with the highest prevalence of SLT use were 1) black females aged 70 and older, 2) black males 65 and older, and 3) white males 15 years of age and older.

In the above analyses, separate attention was given to age comparisons for each race and sex, sex comparisons for each age and race, and race comparisons for each age and sex. This perspective for interpretation was justified by the significant ($P < .01$) results of tests for age-race-sex interactions in two analyses of the data for all persons 10 years old or more and of either race or sex. One of these analyses was based on the maximum likelihood fit of a logistic regression model (6), and the other was based on the weighted least squares fit of a strictly linear model for use (7). Both were undertaken with the CATMOD procedure in the Statistical Analysis System or SAS (8). The presence of the age-race-sex interactions implies that the

TABLE 1.—Use of SLT in 10 SMSA of the southeastern United States by race, gender, and age

Age, yr	White				Black			
	Male		Female		Male		Female	
	Percent use	No.	Percent use	No.	Percent use	No.	Percent use	No.
0-4	0.2	1,372	0.1	1,345	0.0	617	0.0	649
5-9	0.3	1,471	0.0	1,309	0.0	740	0.0	695
10-14	3.5	1,588	0.1	1,533	0.3	670	0.2	655
15-19	11.4	1,664	0.2	1,574	1.4	713	0.0	764
20-24	10.6	1,526	0.5	1,568	1.6	558	0.7	708
25-29	8.8	1,601	0.5	1,736	2.7	520	1.0	724
30-34	7.8	1,721	0.1	1,752	2.6	506	1.9	636
35-39	9.4	1,565	0.4	1,640	4.0	372	2.8	471
40-44	9.7	1,384	0.6	1,438	3.7	298	3.9	438
45-49	10.0	1,029	0.3	1,055	6.2	225	5.0	322
50-54	8.4	1,064	0.8	1,155	9.2	251	5.6	357
55-59	7.8	961	1.2	969	7.0	215	7.8	296
60-64	7.4	914	1.0	1,061	8.4	227	9.3	324
65-69	8.7	733	2.3	912	15.9	189	8.9	248
≥ 70	9.4	1,087	3.9	1,626	11.1	316	18.6	451
Total		19,680		20,673		6,417		7,738

pattern of variation for each factor varies across the levels of the other two and thereby merits separate consideration.

DISCUSSION

Generalization of these findings to other populations and comparisons to future studies of SLT use should be made only with the appropriate considerations. First, these data do not necessarily reflect use in SMSA other than those studied. Second, as described above, information was not available for all households originally identified for study. Third, similar to other large-scale surveys such as the Census, information about all household members was obtained from one adult household member rather than directly from each person for whom we show data. Fourth, in comparing our findings with those from other studies, researchers should also carefully consider the questions that were used. We would have identified more users if we had asked whether SLT had been used within a specified time, such as within 30 days or ever, but we considered such questions to be too specific for respondents who provided information about other household members. Patterns of use across race, gender, and age should be similar for many different measures of its use, and our purpose was to identify those patterns. Finally, the design is cross-sectional, and therefore age and cohort effects cannot be separated. For example, the relatively high use of SLT by black females 70 years of age and older could reflect an increase in use when black women get older or it could indicate that black women who also had high use when they were younger are now in this age group.

CONCLUSIONS

In the households studied, SLT use varied substantially by race, gender, and age. Use generally increased with age for white females, black males, and black females. Among white males, use increased to the 15 to 19 age group and

then remained similar through the oldest age group. Among whites in each age group, males were more likely than females to use SLT. The gender difference pattern was not as consistent for blacks, but when there was a difference, use was greater for males except among those 70 years old and older, an age group in which females were more likely to be users than males. Among males less than 45 years of age, whites were more likely than blacks to use SLT; the races were the same for males aged 50 to 64 and 70 and older, and black males 65 to 69 were more likely than white males of the same age to be users. Among females under 30 years of age, whites and blacks had similar use rates, whereas among older females, blacks were more likely to use it than were whites.

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Native Youth and Smokeless Tobacco: Prevalence Rates, Gender Differences, and Descriptive Characteristics¹

Steven P. Schinke,² Robert F. Schilling II,² Lewayne D. Gilchrist,³ Marianne Rolland Ashby,³ and Eiji Kitajima³

ABSTRACT—This is a report on smokeless tobacco use among Native American youth from Indian reservations in Washington State. Study findings indicate that snuff and chewing tobacco are used frequently, heavily, and at an early age by Native Americans. Nearly one-half of our subjects had used smokeless tobacco on 11 to 20 or more occasions; close to one-third of all the females had used smokeless tobacco on more than 20 occasions. Weekly users in this study were young. Of those Native subjects who used snuff or chewing tobacco weekly, 72% were under 12 years of age. Among youth who reported weekly smokeless tobacco use, about 74% of all females and 90% of all males had first used snuff or chewing tobacco before they were 10 years old. Study results have implications for efforts toward detection, treatment, and prevention of snuff and chewing tobacco use among Native American adolescents.—NCI Monogr 8:39–42, 1989.

The use of SLT poses serious health risks for Native American youth, for there is evidence of early, frequent, and heavy snuff and chewing tobacco use among them and Alaskan Native adolescents (1). Early use of snuff and chewing tobacco may precede later, habitual use of tobacco products (2). On the addictive potential of snuff and chewing tobacco use, the Office of Medical Applications of Research of the National Institutes of Health reported: "Blood levels achieved by smokeless tobacco use are similar to those of cigarette smoking Addicted users of nicotine become tolerant to the drug . . . ; such users increase their dosage until it levels off at one that fulfills their need. Such users need nicotine continually" (3). Emerging data indicate that young SLT users may later switch to cigarette smoking as a source of nicotine (4, 5).

Traditionally, Native American youth have enjoyed low rates of smoking relative to others in minority and majority cultures. However, their early introduction to SLT increases the likelihood of progressing to smoking and longer term addiction. Pollin (6), recalling tobacco use mortality rates, said, "We can conservatively estimate that more than 60% of these yearly deaths do not result from ignorance or from a freely chosen risk . . . but instead represent persons who became addicted to nicotine as adolescents." Nicotine

addiction may be partly responsible for the recalcitrance of SLT habits. Some tobacco users succeed, but most cessation attempts fail, initially and repeatedly (7). Due to these failures, tobacco use relapse rates are higher than for other substances (8).

Added risks of SLT use by Indian youth are implied by patterns of progressive substance abuse when adolescents move into adulthood. One study found "clear temporal developmental stages in the use of licit and illicit drugs from adolescence through young adulthood" (9). Indeed, earlier and more consistently than non-Indian youths, Native American youths progress to and sustain alcohol, drug, and other substance abuse (10–13). To learn more about SLT use among the young Indians, we studied snuff and chewing tobacco use patterns and correlates among early adolescent females and males from Washington Indian reservations.

METHODS

Subjects.—We drew from a representative sample of American Indian reservations in Washington State. Recruited at reservation and tribal schools, recreation centers, and social and health agencies by Indian research assistants and indigenous staff, subjects were eligible for study participation if they were American Indians or Alaskan Natives and if they gave their informed consent.

Of the sample of 119 informed and consenting subjects, who represented 98% of all eligible youths asked to participate in the study, 51 were female and 68 were male. Their ages ranged from 8 to 16 years old; the mean age was 11.3. Most (89%) lived within the boundaries of federally recognized Indian reservations; the remaining subjects lived within a few miles of a reservation. All relied on their respective reservations for educational, health, social, recreational, and commercial services.

Procedure.—In small groups at each site, subjects received a description of the study from the research assistants and staff teachers, counselors, health care professionals, and nonprofessional volunteers. Native staff described the questionnaires that subjects would complete, then outlined provisions for response anonymity and data confidentiality. The youths were assured that their questionnaires and responses would be anonymously masked to preclude knowledge of their identity. Staff further explained how the information obtained would be kept confidential.

Their questions answered, subjects were administered brief, anonymous questionnaires. They were told that their names were not required on the questionnaires and they were free to omit answers on any items. If they had reading difficulties, the staff read the questions aloud and sub-

ABBREVIATION: SLT = smokeless tobacco.

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²School of Social Work, Columbia University, 622 West 113th St., New York, N.Y. 10025. Address reprint requests to Steven P. Schinke, Ph.D.

³School of Social Work, University of Washington, Seattle, Washington 98195.

jects privately recorded their answers. Questionnaires included demographic items about them and their families. Other items asked about their ever and recent use of snuff, chewing, plug, and smoking tobacco and about their tobacco use consumption patterns. The questionnaire had a Cronbach alpha of .79.

For analytic purposes, snuff use was scored positively if subjects reported oral use of moist snuff, dry snuff, or pre-measured snuff packets. Chewing tobacco use was scored positively if they reported use of loose cut, plug, or leaf tobacco products. Smoking tobacco use was scored positively if regular cigarette, cigar, clove cigarette, or tobacco pipe smoking was reported.

RESULTS

By descriptive statistics, study results showed that among Native Americans more than 4 in 5 females and more than 7 in 8 males had ever used snuff or chewing tobacco (table 1). More males than females had used SLT once and between two and five occasions. Smokeless use rates of 11 to 20 occasions were similar for females and males. Heavier SLT use (> 20 occasions) was more prevalent among males. Over one-third of the sample reported SLT use on more than 20 occasions.

More than 83% of all weekly SLT users began their current habit before they were 10 years old. For subjects who reported weekly snuff or chewing tobacco use, the data were categorized by user characteristics. By these findings, female and male weekly SLT users were close in present age (table 2). Compared with females, males began using SLT products at an earlier age.

Although they reported weekly SLT use, over 43% and 47% said that they had used no snuff or chewing tobacco, respectively, in the last 7 days. These discrepancies suggest that subjects who considered themselves weekly users actually used snuff and chewing tobacco less often than weekly. Lending credence to this suggestion are findings of 44 subjects reporting SLT use on over 20 occasions as noted in table 1 relative to the 54 who reported weekly use, as noted in the present age category of table 2.

Of those adolescents who had used snuff in the last 7 days, most (43.7%) had used it between one and five occasions. Gender differences revealed slightly more females than males reporting snuff use on two or more occasions in the past week. Over 50% of the Native American youth who reported chewing any tobacco in the last 7 days had used the product on one to five occasions. Males were more apt than females to report chewing tobacco more than twice

in the last 7 days. Amounts of SLT use reported by subjects were uniformly low for both genders. Finally, 60% of those who said they used SLT in the last 7 days reported having never smoked tobacco. Relative to females, males were inclined to have smoked once. Rates of weekly and daily tobacco smoking did not differ between the genders.

DISCUSSION

These data indicate that among Native American youths from Washington State reservations, snuff and chewing tobacco are used more often by both genders than among comparably aged youths in other minority cultures (14-16). Close to 50% of the Native American adolescent subjects had used SLT between 11 and 20 or more times. Females in this study reported relatively high, although less than males, "ever use" rates of snuff and chewing tobacco. Nearly one-third of all our female participants had used SLT on more than 20 occasions. To date, the heavy ever use frequencies reported for the present female adolescents are the highest rates of SLT use published for young women of any ethnic and/or racial group.

Also noteworthy are study findings on the characteristics of our weekly SLT users. Overall, the sample of weekly tobacco users was young; only 28% of them were more than 12 years old. Understandably, the age at which they reported initial SLT use was similarly young. Among those who reported weekly use, about 74% of the females and 90% of the males had first used snuff or chewing tobacco before the age of 10. Results on participants reporting occasions of snuff and chewing tobacco use in the last 7 days are puzzling. Despite reports that 54 described themselves as weekly users, only 27 and 23 reported any snuff and chewing tobacco use, respectively, in the last 7 days. Possibly, they were exclusively snuff or chewing tobacco users, although this possibility still leaves 4 unaccounted for when tobacco use rates in the last 7 days are subtracted from reports of weekly SLT use. More likely because of the young age represented in our sample, some regarded themselves as weekly users, yet they did not literally use snuff and chewing tobacco every week. Amounts of SLT use reported by the youth indicate fairly light snuff and chewing tobacco habits, relative to adult users. Given their age, however, even these light SLT use patterns are disquieting. Most interesting perhaps were the low rates of tobacco smoking reported by the participants. Only 20% and 17% of the Indian females and males, respectively, reported weekly or daily smoking.

In light of our findings, explanations for snuff and chewing tobacco use among Native American youth warrant consideration. Early adolescents, not unlike their majority culture counterparts, may view SLT use as a rite of passage into adulthood (17-19). Furthermore, smokeless product use patterns observed in this study might reflect the success of advertising by the SLT industry, new and easily used snuff and rolled leaf products, the absence of laws governing the sale and labeling of SLT, and antismoking campaigns (20-24). Deceptively, SLT use may appeal to American Indian youths as a benign substitute for smoking. Whatever the explanation, SLT may introduce these young people to nicotine. The dangers of this introduction were al-

TABLE 1.—SLT use reported by subjects^a

Snuff or chewing tobacco use	Females		Males		Total	
	No.	Percent	No.	Percent	No.	Percent
Never	10	19.6	9	13.2	19	16.0
Once	7	13.7	17	25.0	24	20.2
2 to 5 occasions	4	7.8	8	11.8	12	10.1
6 to 10 occasions	7	13.7	0	0.0	7	5.9
11 to 20 occasions	7	13.7	6	8.8	13	10.9
> 20 occasions	16	31.4	28	41.2	44	37.0

^aPercentages may not add to 100 because of rounding.

TABLE 2.—Characteristics of weekly SLT users^a

Characteristic	Females		Males		Total	
	No.	Percent	No.	Percent	No.	Percent
Present age, yr						
9-10	5	22.7	10	31.3	15	27.8
11-12	12	54.5	12	37.5	24	44.4
13-14	4	18.2	6	18.8	10	18.5
>14	1	4.5	4	12.5	5	9.3
Age at first use, yr						
< 6	2	10.5	7	24.1	9	18.8
6-7	4	21.1	12	41.4	16	33.3
8-9	8	42.1	7	24.1	15	31.3
10-11	3	15.8	3	10.3	6	12.5
>11	2	10.5	0	0.0	2	4.2
Snuff use in last 7 days						
None	9	47.4	12	41.4	21	43.8
Once	2	10.5	6	20.7	8	16.7
2 to 5 occasions	5	26.3	7	24.1	12	25.0
>5 occasions	3	15.8	4	13.7	7	14.6
Chewing tobacco use in last 7 days						
None	8	50.0	13	46.6	21	47.7
Once	4	25.0	2	7.1	6	13.6
2 to 5 occasions	2	12.5	9	32.1	11	25.0
>5 occasions	2	12.5	4	14.3	6	13.6
Cans, pouches, plugs used weekly						
<1	7	46.7	9	31.0	16	36.4
1	7	46.7	16	55.2	23	52.3
2 to 4	1	6.7	3	10.3	4	9.1
>4	0	0.0	1	3.4	1	2.3
Current tobacco smoking						
Never smoked	12	60.0	18	60.0	30	60.0
<Monthly	3	15.0	7	23.3	10	20.0
Monthly	1	5.0	0	0.0	1	2.0
Weekly	1	5.0	2	6.7	3	6.0
Daily	3	15.0	3	10.0	6	12.0

^aPercentages within each category exclude missing data and may not add to 100 because of rounding.

ready noted in the National Institutes of Health report on the addictive nature of nicotine in SLT products. Though Native Americans have sustained relatively low rates of tobacco smoking in the past, compared with other groups of Americans, increased use of snuff and chewing tobacco by Indian adolescents may foreshadow the increased use of smoking tobacco. A recent report by the Department of Health and Human Services (25) thus warned, "The smoking prevalence of Native American youth needs to be more closely monitored, as an indicator of future risk for smoking-related cancers."

Without proving causality, data reported in this study could direct efforts of civilian and public health authorities to prevent snuff and chewing tobacco use among young American Indians. Besides directly reducing health risks, efforts to prevent SLT use could reduce their risk of other substance use. Moreover, as Jessor (26) observed, "Adolescence is a pivotal stage in the life span for the development of health-related behavior. Not only is it a period of heightened health risk, but what happens in adolescence is consequential for health in later life." For Native American adolescents, interventions to prevent tobacco use could bring lasting returns.

More research is needed on snuff and chewing tobacco use among these adolescents. The present study was limited to youths from reservations in Washington State. In the absence of biochemical validation procedures, study subjects may have underreported or overreported their snuff and chewing tobacco use (27-29). To be sure, the present sample was not large and thereby could be unrepresentative of the Native American adolescent pattern nationwide. Future studies with new and larger samples are needed for verification of our present findings. Culture-specific preventive intervention research on SLT use among American Indian youth seems timely. Epidemiologic studies that will help us better understand and guide such prevention efforts also appear worthwhile. Perhaps the data reported here will stimulate new research of snuff and chewing tobacco use among this group of young Americans.

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Parent Characteristics, Perceived Health Risk, and Smokeless Tobacco Use Among White Adolescent Males¹

Karl E. Bauman, Gary G. Koch, and G. Michael Lentz^{2, 3}

ABSTRACT—The results of this study indicate that father education, father use of smokeless tobacco, and adolescent risk perception contribute to the use of smokeless tobacco by white males 12 to 14 years of age. However, risk perception does not account for the correlation between parent characteristics and child behavior. Father education and child smokeless tobacco use are inversely related if the father does not use it, and they are directly related if the father does; this finding is consistent with theories of modeling but is contrary to the common observation that the use of some abusive substances is relatively low among adolescents in higher social and economic levels. We concluded that father characteristics should be considered in research and in programs pertaining to the use of smokeless tobacco by white adolescent males.—NCI Monogr 8:43-48, 1989.

The behavior of children often is influenced by characteristics of their parents. However, no research has been reported that 1) tested for an association between parent educational attainment and SLT use by children or 2) examined the relationship between parent and child use of snuff and chewing tobacco. One reason that parent characteristics have not been studied is that nearly all data on adolescent SLT use have been collected from children in schools. Many children were either unable to report parent educational attainment and SLT use or child reports of parent characteristics were considered to be too inaccurate.

For our research on adolescents, we asked their mothers for information on parent educational attainment and SLT use. We limited our hypotheses to white males because few of our subjects in other race-gender groups use SLT. One hypothesis was that its use by white male adolescents is inversely related to parent educational attainment. A second hypothesis was that adolescent and father use are directly related.

Another of our purposes was to determine whether the adolescent's perception of the harmful health effects of SLT explains associations between parent characteristics and its use by adolescents. Regarding parent educational attain-

ment, our reasoning is that advanced education is associated with many attributes that might instill the expectation of the harmfulness of SLT. For example, parents with advanced education might be more exposed to information about its harmful effects, and they might spend more time encouraging their children to behave in healthful ways. Thus, as parent educational attainment increases, children might be more likely to expect unhealthful effects from SLT, and that expectation might reduce their use.

The risk perceived from SLT also could explain a relationship between its use by fathers and their children. For example, children might believe that their fathers do not engage in harmful behaviors, and therefore adolescents with fathers who use SLT might believe that such behavior is not harmful. Thus adolescents whose fathers use SLT might be more likely to use it than adolescents whose fathers do not. Other variables might also explain the connection between parental characteristics and SLT use by adolescents, but here we consider only the harm expected.

The above reasoning assumes that the relationship is inverse between the expectation of harmful effects from these tobacco products and their use. That assumption is supported by earlier studies (1, 2), and it is tested again with our data. Moreover, because school-based studies have been reported in which adolescent use increases with grade in school (3), we included adolescent age in these analyses to assess its possible role as a confounder. Age is considered rather than grade in school because age was a sampling criterion and grade in school was not.

METHODS

The data reported here are from a field experiment that was conducted for evaluation of the influence of a mass media campaign on the prevention of the onset of adolescent cigarette smoking. Ten SMSA, which are similar in social and demographic characteristics and spread throughout the southeastern United States, are in the experiment. Adolescents aged 12 to 14 years and their mothers served as the focal subjects. For the baseline surveys conducted within each SMSA from April 1, 1985, through October 13, 1985, approximately 80 clusters of households with approximately 2.8 adolescent subjects per cluster were randomly selected, and interviewers attempted to obtain data from all eligible subjects in those households. When more than 1 age-eligible adolescent resided in a household, 1 was randomly chosen to serve as a subject. For these analyses, the data are aggregated for the 10 SMSA.

Of the 2,534 adolescent subjects in the clusters who were eligible for study, 2,105 (83.1%) participated. Subjects av-

ABBREVIATIONS: SLT = smokeless tobacco; SMSA = Standard Metropolitan Statistical Area(s).

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²School of Public Health, CB #7400, Rosenau Hall, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599. Address reprint requests to Karl E. Bauman, Ph.D.

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eraged 1 hour to complete a self-administered questionnaire in their homes and provided alveolar breath and saliva samples for measurement of cigarette smoking behavior. The mothers of most adolescents also completed (average 25 min) a self-administered questionnaire and provided alveolar breath samples. The 36 adolescents who were Asian, Hispanic, or American Indian were excluded from these analyses because there were too few for separate consideration and because other studies (3) indicate that the SLT use by these groups could differ substantially from the whites and blacks who make up nearly all of our sample. The 34 adolescents for whom information was missing on SLT use were also excluded from these analyses.

The adolescents were asked when they had last used chewing tobacco or snuff. Following a convention adopted by others (3), we classified those who had used these products within 7 days as users. One hundred nine (14.7%) of the 741 white adolescent males were users. In the other race-gender groups, use was much less: Only 8 of the 697 white females, 2 of the 309 black females, and 10 of the 288 black males were users. Thus we limited the analyses to white males.

Fifty-nine white males were excluded because questionnaires were not completed by their mothers; an additional 78 were excluded because there was no information for a father or father-like figure living in the home. Thirty other subjects were dropped because information was missing on parent educational attainment, parent SLT use, or perception of health risk. Therefore, the analyses are based on a sample of 574 white males for whom complete information was obtained.

The mothers were asked to indicate how many times they had used chewing tobacco or snuff in the last 30 days; those who had were classified as users. Mother use of SLT was excluded as a variable from these analyses because only 3 of the 574 mothers were users. Mothers responded to the same question about SLT use for the adolescent's father or father-like figure to the adolescent who was living in the home. Of the 574 fathers, 15.2% were classified as users by virtue of their use within the last 30 days.

The mothers also were asked to report their educational attainment and that of the adolescent's father. The adolescents were asked the same questions about the educational attainment of their parents. Answers were recorded among six categories ranging from "didn't graduate from high school" to "more than 4 years of college (graduate school)." The categories were collapsed to represent three levels: did not complete high school, high school graduate, and college graduate. These three levels were chosen because they were meaningful and yielded the optimal agreement between the child and parent. The agreement was 86.6% for the 461 adolescent-mother pairs with information from child and mother, and 85.0% for the 448 adolescent-father pairs with information from child and mother. For analyses in this paper, we use the mothers' reports of parent educational attainment, except when their reports were unavailable; we used the adolescents' reports of parent educational attainment for 19 mothers and 21 fathers.

To measure perception of health risk, we asked our subjects, "How harmful to health is using chewing tobacco

or snuff?" The response categories were "very harmful," "somewhat harmful," "not very harmful," and "not at all harmful." The latter two categories were combined because only 10 (1.7%) of our 574 white male subjects considered SLT to be harmless.

The multivariate statistical analysis technique we used required each study case to have information for all variables. Therefore, as described above, the subjects for whom information was missing on any study variable were excluded. Loss of cases can produce bias due to attrition. We assessed that source of bias by comparing the results of all the bivariate analyses presented in this paper with the results of parallel analyses that used cases with available information for each variable in a pair but not necessarily with information for all other study variables. The results were so similar that we do not show them here, and we assume that our conclusions were not influenced by attrition.

RESULTS

Adolescent Use

The relationships between parent educational attainment and adolescent use of SLT are shown in table 1. As hypothesized, its use by children decreases with higher levels of parent education. Use decreases from 22.0% when fathers are not high school graduates to 8.9% when fathers graduated from college ($\chi^2 = 9.28$, $P < .01$). Use decreases from 17.7% when mothers are not high school graduates to 6.5% when mothers graduated from college ($\chi^2 = 6.04$, $P < .05$).

The hypothesis that the association between father and child use of SLT is related is confirmed (table 1). Nearly one-quarter (24.1%) of the adolescents whose fathers use SLT are users, whereas 12.9% of the adolescents whose fathers do not use SLT are users ($\chi^2 = 7.41$, $P < .01$).

The relationship between the amount of harm adolescents expect from SLT and its use is strong ($\chi^2 = 43.39$, $P < .001$), as hypothesized. As shown in table 1, 32.0% of the adolescents who believe that SLT is not very harmful use it, whereas use is 16.5% and 4.8% for those who consider the products to be somewhat harmful and very harmful, respectively.

An association between adolescent use of SLT and age (table 1) was suggestive but not significant by the Pearson chi-square ($\chi^2 = 4.87$, $P = .088$). However, the correlation chi-square (4) for assessing trends indicated that use significantly increases with age ($\chi^2 = 4.73$, $P < .05$). The perception of harmful effects from SLT also decreases with age (table 2). Thus age is considered as a possible confounder in the multivariate analyses discussed below.

Parent Characteristics and Perceived Health Risk

For perceived harm to explain the relationships between parent characteristics and adolescent use, the parent characteristics must be related to adolescent expectation of harm (table 2). Father education, mother education, and father use of SLT are significantly associated with adolescent expectation of harm from it. Of the adolescents whose fathers use SLT, 27.6% consider it to be very harmful, and among adolescents whose fathers are not users, 42.1% consider it to be very harmful ($\chi^2 = 6.48$, $P < .05$). The signifi-

TABLE 1.—Adolescent use of SLT by parent characteristics, risk perception, and age

Parent characteristics, risk perception, age	User, %	Nonuser, %	No. of subjects	χ^2	
				Pearson	Rank correlation
Father education					
<High school	22.0	78.0	118	9.28 ^a	9.14 ^a
High school graduate	14.7	85.3	299		
College graduate	8.9	91.1	157		
Mother education					
<High school	17.7	82.3	113	6.04 ^b	4.58 ^b
High school graduate	15.7	84.3	369		
College graduate	6.5	93.5	92		
Father					
User	24.1	75.9	87	7.41 ^a	7.40 ^a
Nonuser	12.9	87.1	487		
Adolescent risk perception					
Not very harmful	32.0	68.0	103	3.39 ^c	41.75 ^c
Somewhat harmful	16.5	83.5	242		
Very harmful	4.8	95.2	229		
Age, yr					
14	18.8	81.2	202	4.87 ^d	4.73 ^b
13	13.5	86.5	215		
12	10.8	89.2	157		

^a $P < .01$.^b $P < .05$.^c $P < .001$.^d $P = .088$ (not significant).

cant associations involving education are not linear. Specifically, when considering father or mother educational levels, the percentages of adolescents perceiving SLT as not very harmful and very harmful decrease with increased education, whereas the percentages of those who consider SLT somewhat harmful increase with higher educational levels.

Multivariate Analyses

The relationship of adolescent use of SLT to father and mother education, father use, and adolescent perception of harm from SLT was analyzed in a multivariate sense with logistic regression methods (5). Adolescent age also was

TABLE 2.—Adolescent risk perception by parent characteristics and adolescent age

Parent characteristics, adolescent age	Risk perception			No. of subjects	χ^2	
	Not very harmful	Somewhat harmful	Very harmful		Pearson	Rank correlation
Father education						
<High school	30.5	24.6	44.9	118	25.97 ^a	.44 ^b
High school graduate	15.7	45.2	39.1	299		
College graduate	12.7	49.7	37.6	157		
Mother education						
<High school	20.4	29.2	50.4	113	15.07 ^c	1.17 ^b
High school graduate	19.0	43.1	37.9	369		
College graduate	10.9	54.4	34.8	92		
Father						
User	21.8	50.6	27.6	87	6.48 ^d	5.55 ^d
Nonuser	17.3	40.7	42.1	487		
Age, yr						
14	19.8	48.0	32.2	202	16.71 ^c	12.48 ^a
13	19.5	42.8	37.7	215		
12	13.4	33.8	52.9	157		

^a $P < .001$.^b Correlation is not significant.^c $P < .01$.^d $P < .05$.

considered as a potential explanatory factor. Application of logistic regression enables each member of a set of explanatory variables to have its association with adolescent use of SLT evaluated in a setting that accounts for the roles of other explanatory variables. It also provides a prediction equation for a description of the relationship of adolescent use with a set of explanatory variables. Our objectives in conducting the logistic regression analyses were as follows:

- 1) To identify a subset of explanatory variables among father education, mother education, father use of SLT, and adolescent age that account for their association with adolescent use of SLT;
- 2) To assess whether interaction effects among the explanatory variables identified in objective 1 are associated with adolescent use of SLT;
- 3) To assess whether adolescent perception of harm from SLT is associated with its use when the explanatory variables from objective 1 and the interactions from objective 2 are taken into account;
- 4) To evaluate the extent to which accounting for adolescent perception of harm influences the association of adolescent use of SLT with the explanatory variables from objective 1 and their interactions from objective 2;
- 5) To evaluate whether interaction effects between adolescent perception of harm and the explanatory variables from objective 1, or higher order interactions among these variables, are associated with adolescent use of SLT.

For objective 1, stepwise methods were used. This process identified father education, father use of SLT, and the age indicator for 14 years versus 12 or 13 years as having significant ($P < .05$) associations with adolescent use of SLT for the setting that included all three of these explanatory variables. Mother education was clearly nonsignificant ($P = .43$) in this setting, and so its role is encompassed by the other three variables. The regression coefficients and P -values for this first model are shown in table 3.

To address the interaction effects of adolescent use, we

initially forced the explanatory variables into the logistic regression model and then applied stepwise methods to determine whether their interactions, as expressed by "pairwise cross-products," would qualify for entry to the model. This analysis indicated that only the interaction of father education with father use of SLT was significant ($P < .01$). Specifically, adolescent use decreased as father education increased for adolescents whose fathers did not use SLT, but for adolescents whose fathers did, adolescent use increased as father education increased. Thus this interaction indicates that adolescent and father behavior with SLT becomes more similar as father education increases. The statistical results for this second model are also given in table 3.

The role of adolescent risk perception was evaluated relative to objective 3 by its inclusion in the models from objectives 1 and 2; i.e., the model with father education, father use of SLT, and adolescent age, and the previously stated model plus the interaction of father education and use. For each of these frameworks, the negative association between adolescent use and adolescent expectation of harm was significant ($P < .01$); adolescent use decreased as the expectation of harm increased. Within these models, father education, father use, and the interaction of father education and father use also were significant ($P < .01$), but the association with age was nonsignificant ($P = .12$). In relation to objective 4, adolescent perception of harm does not fully encompass the association of adolescent use of SLT with father education, father use, and the interaction between these two variables. Indeed, the estimates for models with and without expected harm as seen in the second and third models of table 3 are so similar that the role of harm perception as an intervening variable must be considered negligible. Also, adolescent age does not need to be included in the logistic regression model with the previously mentioned explanatory variables. Further assessment of this model relative to objective 5 indicated that no interactions involving adolescent perception of harm needed to be added to the model.

For the final model with father education, father use of

TABLE 3.—Results for logistic regression models

Explanatory variable ^a	Entry as first variable, <i>P</i>	Model					
		First		Second		Third	
		Estimate	<i>P</i>	Estimate	<i>P</i>	Estimate	<i>P</i>
Reference intercept	^b	-1.16	.003	-0.35	.415	0.81	.073
Father education	.002	-0.48	.007	-0.88	<.001	-0.83	<.001
Father use	.006	0.65	.027	-2.67	.004	-2.98	.002
Father education-father use interaction	^c	^c		1.80	<.001	1.88	<.001
Adolescent risk perception	<.001	^c		^c		-1.03	<.001
Age indicator for 14 yr	.037	0.57	.020	0.46	.066	^d	
Mother education	.030	^d		^d		^d	

^a The explanatory variables were: father and mother education (1 if less than high school graduate, 2 if high school graduate or some college, 3 if college graduate or more); father use of SLT (0 if no, 1 if yes); adolescent age (0 if 12 or 13, 1 if 14); and adolescent risk perception for SLT (0 if not very harmful, 1 if somewhat harmful, 2 if very harmful).

^b Variable was not applicable.

^c Variable was not eligible.

^d Variable was not included in analyses.

SLT, the interaction of father education and father use, and adolescent perception of harm, the estimates of the regression coefficients can be used to form a prediction equation for adolescent use of SLT. The form of this prediction equation is as follows:

Prevalence of adolescent use of SLT =

$$\frac{\exp \{0.81 - 0.83(\text{FE}) - 2.98(\text{FU}) + 1.88(\text{FE})(\text{FU}) - 1.03(\text{ARP})\}}{1 + \exp \{0.81 - 0.83(\text{FE}) - 2.98(\text{FU}) + 1.88(\text{FE})(\text{FU}) - 1.03(\text{ARP})\}}$$

where exp denotes the exponential operator, FE is father education, FU is father use, and ARP is adolescent risk perception. Predicted prevalences from this equation for the cross-classification of adolescents according to father education, father use, and adolescent expectation of harm are shown in table 4; the corresponding observed sample sizes and prevalences are also shown. Adolescent use of SLT decreases as perception of harm increases for all situations of father education and use. For the adolescents whose fathers are not at least high school graduates, their use is less if their father uses SLT, but for those whose fathers are at least high school graduates, use is greater if their fathers are also users. Use by adolescents whose fathers do not use SLT decreases as father education increases, but for those whose fathers are users, it increases as father education increases.

DISCUSSION

Our findings clearly indicate that father education and use of SLT are related to its use by white adolescent males. These explanatory variables were not included in earlier studies of SLT use by young people, and that might explain why other variables, which have received more consideration by research, such as peer influence (1, 6, 7), have been given more attention in recommendations for interventions designed to influence that behavior (8). Our findings clearly suggest that family variables merit attention by programs and research that focus on adolescent SLT use.

Many previous studies of the use of abusive substances

by adolescents have also found inverse correlations between parent educational attainment and behavior, but they did not test for interactions and therefore could not detect the major qualification to that main effect that was revealed by our data: The relationship between father education and adolescent use of SLT is in opposite directions for those whose fathers do and do not use it. This finding underscores the importance of parent characteristics for an understanding of the reason adolescents use SLT and demonstrates the need for testing interactions when these variables are involved.

We interpret the interaction involving parent educational attainment and behavior in the context of social learning theory. "With regard to the characteristics of models, those who have high status, competence, and power are more effective in prompting others to behave similarly than are models of lower standing" (9). Thus, among white male children with fathers who use SLT, those with fathers who attained higher educational levels are also more likely to use SLT themselves than are those whose fathers have less education. Among children whose fathers do not use SLT, those whose fathers had relatively little education are more likely to differ from their fathers in its use and tend to be influenced by factors other than the behavior of their fathers. Social learning theory also suggests that adolescents in higher socioeconomic families have personal characteristics that make them particularly responsive to models (9).

The harm that adolescents expect from SLT is clearly related to their use. However, contrary to the reasoning that guided the analyses, adolescent risk perception does not explain the association between adolescent use of SLT and parent characteristics. Other variables need to be identified as intervening variables. Moreover, mother education does not make an independent contribution to its use by white adolescent males.

Two caveats are necessary. First, our data are cross-sectional and therefore the causal direction for some relationships cannot be determined. This does not pose a problem for the interpretation of some of our findings. For example, we comfortably conclude that father education

TABLE 4.—Adolescent SLT use by father education, father use of SLT, and risk perception

Sample size and prevalences	Father education	Adolescent risk perception					
		Not very harmful		Somewhat harmful		Very harmful	
		Father use		Father use		Father use	
		No	Yes	No	Yes	No	Yes
Sample size	<High school	27	9	18	11	40	13
	High school graduate	39	8	110	25	108	9
	College graduate	18	2	70	8	57	2
Observed prevalence, %	<High school	44.4	33.3	38.9	0.0	10.0	0.0
	High school graduate	25.6	50.0	15.5	32.0	3.7	11.1
	College graduate	16.7	50.0	7.1	37.5	1.8	50.0
Predicted prevalence, % ^a	<High school	49.5	24.8	26.0	10.5	11.2	4.0
	High school graduate	30.0	48.5	13.3	25.3	5.2	10.8
	College graduate	15.7	73.0	6.3	49.2	2.3	25.8

^a Prevalence was derived from logistic regression model.

might influence adolescent use of SLT, and adolescent use does not contribute to level of education attained by the father. However, panel data are necessary for establishment of the temporal relationships of some variables. Although we have reasoned that adolescent risk perception influences behavior with SLT and father use contributes to that by the child, it is plausible that SLT use at least partly contributes to the formation of attitudes about such behavior, and use by the adolescent contributes to that of the father. The second qualification to our findings is that one should exercise caution when generalizing beyond subjects like those in this study.

CONCLUSIONS

For the white adolescent males studied, use of SLT increases if the father is also a user. Multivariate analyses revealed that 1) mother education is not independently related to adolescent use; 2) perceived risk is related to parent characteristics and to adolescent use, but it does not account for relationships between parental characteristics and adolescent use; and 3) the direction of the relationship between father education and adolescent use depends on whether the father uses SLT: If the father is a user, adolescent use increases with father education, whereas if the father is not, adolescent use decreases with father education. We conclude that father characteristics contribute to the explanation of SLT use by young white males.

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Use of Smokeless Tobacco Among Male Adolescents: Concurrent and Prospective Relationships¹

Dennis V. Ary^{2, 3}

ABSTRACT—The concurrent and prospective correlates of the use of smokeless tobacco among 846 adolescent males were examined. There were 6- and 12-month follow-ups to the initial questionnaire. Substantial levels of tobacco, alcohol, and marijuana use were reported, with 21% reporting use of more than one drug in the last week. Daily smokeless tobacco users were more likely to initiate use of cigarettes, marijuana, and alcohol than were other males. In addition, the "having used" smokeless tobacco variable was related to increased use of cigarettes, marijuana, and alcohol at follow-up. Discriminant analysis of concurrent data identified peer use of smokeless tobacco and experience with cigarette smoking as the primary discriminating factors between males who had tried it and those who had not. Peer use of smokeless tobacco also discriminated between daily users and those who had tried it but had not gone on to become daily users. Thus peer influence seems to be an important factor not just in trial of smokeless tobacco but also in the development of a daily use pattern. Beginning use of smokeless tobacco was related to offers to use alcohol, cigarettes, and marijuana; peer use was the best predictor of continued daily use.—NCI Monogr 8:49-55, 1989.

Considerable evidence has been accumulated on the significant health consequences of regular use of SLT (1, 2). In addition, significant increases in its use by adolescent males have recently been reported (3, 4). Unfortunately, little is known about the psychosocial factors associated with the use of the substance by adolescents. In this study, the replicability of findings from our prior work on SLT issues was tested. Previously, we (5) found that SLT use among adolescent males was related to the concurrent use of alcohol, marijuana, and cigarettes and that it represented a prospective risk factor for the onset or increased use of those substances. Moreover, peer use of SLT was identified as the primary factor discriminating between male adoles-

cent users and nonusers. Factors such as having tried smoking, the intention to smoke in the future, and peer use discriminated male adolescents who tried SLT and those who did not. The prospective predictors of the onset and continued use of SLT were also examined. Each of these issues is reexamined with a different subject sample of similar ages. Convergence between the 2 studies would enhance confidence in the validity of the findings and move us closer to an understanding of the factors and processes associated with the use of SLT.

METHODS

Participants in this study were 1,676 students from two school districts in Oregon. There were 459 male and 417 female seventh-grade students from six middle schools, and 387 male and 413 female ninth- and tenth-grade students from three high schools. As part of the evaluation of a smoking prevention program in these schools, the students completed a questionnaire. They were reassessed 6 months later and again at 12 months. The initial assessment was completed during the fall of 1981.

The questionnaire was administered in health classes. Each student's parents were sent a postage-paid consent letter, which they were to return if they did not want their child assessed; only 1.4% did so. All students were requested to provide breath and saliva samples and were informed that the samples would be analyzed to determine their smoking status. This physiologic sample procedure was expected to increase the accuracy of self-reported smoking (6, 7). The students were informed that their participation was voluntary and they could decline to participate at any time; 2.6% of the students declined.

The questions concerned subject use of cigarettes, SLT, marijuana, and alcohol, and about offers the student may have received to use cigarettes, marijuana, and alcohol. Three items pertained to SLT use: "I have tried chewing tobacco or snuff once or twice," "Are you a daily user of chewing tobacco or snuff?" "How many of your friends use chewing tobacco?" Additional items asked about subject intention to smoke in the future and about parental, sibling, and peer smoking behavior. One item asked if the subject had ever tried smoking cigarettes. We developed a scale of smoking experience by counting the affirmative responses to 10 items, ranging from "I have felt like trying a cigarette," through "I have had one or more puffs on a cigarette," to "I smoke but no more than one cigarette a week."

Although this questionnaire did not inquire about the form of SLT used, our subsequent surveys established that the predominant form in these schools has been moist snuff

ABBREVIATION: SLT = smokeless tobacco.

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² Oregon Research Institute, 1899 Willamette St., Eugene, Oregon 97401.

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(1). A small amount (i.e., a dip or pinch) of moist snuff is typically placed between the gums and the mucosa of the lower lip or cheek.

RESULTS

Prevalence and Stability of Smokeless Tobacco Use

Sixty-eight percent of the males and 18.5% of the females in the sample reported having used SLT in their lifetime. Similarly, 14.0% of the males and 0.7% of the females indicated that they used it daily. The extremely low female daily use rate suggests that SLT does not represent a serious substance abuse problem for female adolescents at this time. Consequently, such data for females will not be examined in great detail here.

In light of reports that smoking by adolescent males may be lower than for females (8), we determined if this is offset by increased use of SLT among male adolescents. A chi-square analysis of the relationship between gender and daily use of any tobacco product indicated that a significantly higher proportion of males report daily use of some form of tobacco product than do females, $\chi^2 (1; n = 1,625) = 30.2, P < .0001, \phi = .14$. Of the girls participating, 8.2%

reported daily smoking, an additional 0.4% indicated daily SLT use, and 0.4% reported daily use of both substances. Thus 9.0% of the females reported tobacco use. Of the 18.4% males reporting daily tobacco use, 4.4% indicated daily cigarette use, an additional 12.6% acknowledged daily use of SLT, and 1.3% indicated both. A similar pattern emerges when those who smoke less frequently are included in this analysis. For the females, 14.6% reported smoking in the last week and/or daily use of SLT; for males, it was 21.6%. This difference was also significant, $\chi^2 (1; n = 1,625) = 13.1, P < .0003, \phi = .09$. The number of daily users of SLT was nearly three times that of daily smokers among the males.

Data related to the stability of SLT use among males are displayed by grade level in table 1. Among the participants who reported at initial assessment that they had never tried it, at 12-month follow-up 25.4% indicated that they had tried it and 1.5% acknowledged daily use. All those who became daily users were seventh graders. Among the students who reported having tried SLT at initial assessment, 7.1% acknowledged that they were daily users at the 6-month follow-up. At the 12-month follow-up, 9.4% had become daily users. Regarding the stability of use among this group, 70.9% continued use daily at the

TABLE 1.—Stability of SLT use by adolescent males at 6- and 12-month follow-up

Follow-up	SLT use category at initial assessment	Percent of students in each use category					No. of students/grade
		Initial grade level	Never tried	Tried, not daily user	Daily user	Percent of grade total	
At 6 mo	Never tried	7	70.1	28.4	1.5	37.2	134
		9	80.4	19.6	0.0	29.3	56
		10	91.7	8.3	0.0	27.6	24
		All	75.2	23.8	0.9	33.5	214
	Tried, not daily user	7	—	92.2	7.8	53.6	193
		9	—	95.0	5.0	52.9	101
		10	—	90.9	9.1	50.6	44
		All	—	92.9	7.1	53.0	338
	Daily user	7	—	42.4	57.6	9.2	33
		9	—	23.5	76.5	17.8	34
		10	—	15.8	84.2	21.8	19
		All	—	29.1	70.9	13.5	86
	Percent of grade total	7	26.1	63.9	10.0	100.0	360
		9	23.6	60.2	16.2	100.0	191
		10	25.3	51.7	23.0	100.0	87
		All	25.2	61.1	13.6	100.0	638
At 12 mo	Never tried	7	71.7	26.0	2.4	39.0	127
		9	76.0	24.0	0.0	27.8	50
		10	75.0	25.0	0.0	34.3	24
		All	73.1	25.4	1.5	34.9	201
	Tried, not daily user	7	—	88.2	11.8	52.1	170
		9	—	91.8	8.2	54.4	98
		10	—	100.0	0.0	42.9	30
		All	—	90.6	9.4	51.7	298
	Daily user	7	—	31.0	69.0	8.9	29
		9	—	15.6	84.4	17.8	32
		10	—	25.0	75.0	22.9	16
		All	—	23.4	76.6	13.4	77
	Percent of grade total	7	27.9	58.9	13.2	100.0	326
		9	21.1	59.5	19.4	100.0	180
		10	25.7	57.2	17.1	100.0	70
		All	25.5	58.9	15.6	100.0	576

6-month follow-up, and 76.6% reported continued daily use at the 12-month follow-up. The proportion of daily users of SLT who continue to use it seems high. In comparison, the proportion of male daily cigarette users in this study who reported continued daily smoking at the 12-month follow-up was only 30%. This difference in proportion of daily SLT users versus daily cigarette smokers is significant, $z = 3.7$, $P < .002$. On the basis of these data, once an adolescent male has established a pattern of daily SLT use, he is 2.5 times more likely to continue than is a daily cigarette smoker.

Concurrent Correlates of Smokeless Tobacco Use Among Males

In this study, factors that differentiate SLT user groups were identified by stepwise discriminant analysis methods. In the discriminant analyses, variables were entered in the discriminant function only if they resulted in a significant increase in the generalized distance measure of group separation, Rao's V . In these analyses, each of the variables entered also accounted for a significant change in Rao's V even after all the other variables in the function had been entered. That is, each variable included in the discriminant function made a unique contribution.

Some of the variables had highly skewed distributions (e.g., number of cigarettes smoked in the last week). A separate set of discriminant analyses was performed with the use of the log transform of these variables. The results of these analyses did not substantively differ from the analyses of the untransformed variables. Consequently, the untransformed analyses are presented below.

Factors Related to Trying Smokeless Tobacco

To develop effective intervention methods to prevent the onset of SLT use among adolescent males, researchers must determine which factors influence the youths to try it. Table 2 presents the results of a stepwise discriminant analysis to distinguish between the males in this sample who tried SLT and those who did not. The analysis indicated that considerable discriminating power was present in the variables utilized. The Wilks' λ of .78 was significant ($P < .0001$), and the shared or explained variance was 22%. The derived function correctly classified 74% of all subjects. The standardized discriminant function coefficients are listed to indicate the relative weights assigned to variables in defining the discriminant function. These standardized coefficients are similar to standardized regression coefficients in linear regression analysis. Each of the variables accounted for a significant change in Rao's V , even when entered last in the function. The structure coefficients are also shown because they are the correlations between the predictor variables and subject discriminant scores. Variables with high structure coefficients discriminate well between subject groups. Clear interpretation is facilitated by the listing of only structure coefficients greater than .30. Based on the structure coefficients in this analysis, "experience with smoking" and "number of friends using SLT" are important discriminators between those who try it and those who do not.

Additional discriminant analyses were performed for determination of whether the discriminating variables for seventh graders differed from those for ninth and tenth graders.

For both groups of students, the variables with the highest structure coefficients were: "number of friends using SLT," "level of smoking experience," and "tried smoking."

Factors Discriminating Triers From Daily Users

Beyond preventing the onset or trying of SLT, preventing adolescents who have tried the substance from continuing its use is also a relevant issue for those involved in cessation programs. A discriminant analysis determined which concurrent variables distinguished between male triers who have gone on to become daily users and those triers who have not become daily users. The analysis yielded a significant Wilks' λ of .75, $P < .0001$ (table 2). The discriminant function explained 25% of the variance and correctly classified 83% of the subjects. The structure coefficients clearly indicate that number of friends using SLT is related to whether these adolescents go on to become daily users or not. The use of alcohol also appears to be a notable predictor.

Separate analyses were done for the seventh graders and the ninth and tenth graders, so that any differences in the discriminating factors could be determined. In both groups, the primary discriminator was number of friends using SLT.

Factors Discriminating Daily Users From Never Users

An analysis to differentiate daily users from those who have never tried might be expected to underscore their differences more clearly. As shown in table 2, the measured variables did discriminate well and accounted for 61% of the variance with a significant Wilks' λ of .39. The function correctly classified 90% of the subjects. Again, the structure coefficients indicate that number of friends using SLT was the primary predictor.

Prospective Correlates of Smokeless Tobacco Use Among Males

Predictors of Smokeless Tobacco Onset

The ability to predict the onset of SLT use among males who have never used the substance may be valuable in our targeting "at-risk" individuals for selective intervention. Discriminant analysis of the 6-month data yielded no significant predictors. The analysis of the 12-month data showed significant univariate prediction (Rao's $V > 4.0$, $P < .05$) for: number of offers of alcohol, offers of cigarettes, offers of marijuana, number of alcohol uses, and number of cigarette offers accepted. When number of offers of alcohol was entered first in the function, none of the other variables resulted in significant additional change in Rao's V , and they were not added to the equation. With only the offers of alcohol in the function, the significant Wilks' λ was .96, $P < .003$. The relationship of offers to use of these substances and subsequent use of SLT was consistent, although the explained variance was small, 4.3%.

Predictors of Change in Daily Use of Smokeless Tobacco

Central to any SLT cessation effort is a greater understanding of the factors related to change in use patterns. The predictors of change in the pattern of daily use were examined with discriminant analysis so those factors could be identified that differentiated males who remained daily users at follow-up from those who did not. Of the

TABLE 2.—Concurrent discriminant analyses of SLT use among adolescent males

Predictor variables	Tried chewing tobacco or snuff ^a		Daily users vs. triers ^b		Daily users vs. never used ^c	
	Standardized coefficients	Structure coefficients	Standardized coefficients	Structure coefficients	Standardized coefficients	Structure coefficients
No. of friends using SLT	.52	.66	.86	.93	.76	.84
Tried smoking	.34	.67	—	—	—	.31
Level of smoking experience	.46	.72	.26	.34	.44	.49
Intention to smoke	—	.35	—	—	—	—
No. of cigarettes last wk	—	—	—	—	—	—
No. of cigarettes yesterday	—	—	—	—	—	—
No. of cigarette offers last wk	-.18	—	—	—	-.22	—
No. of cigarette offers accepted last wk	—	—	—	—	—	—
Best friend smokes	—	—	—	—	—	—
No. of friends smokers	—	.37	—	—	—	.33
Father smokes	—	—	—	—	—	—
Mother smokes	—	—	—	—	—	—
No. of brothers smoke	—	—	—	—	—	—
No. of sisters smoke	—	—	—	—	—	—
No. of marijuana uses last wk	—	—	—	—	—	—
Use marijuana daily	—	—	—	—	—	—
No. of marijuana offers last wk	—	.32	—	.32	—	—
No. of alcohol uses last wk	—	.43	.22	.48	.18	.49
Use alcohol daily	—	—	—	—	—	—
No. of alcohol offers last wk	.29	.48	—	.38	.22	.48
Summary statistics						
Total Wilks' λ	.78		.75		.39	
Significance of λ	$P < .0001$		$P < .0001$		$P < .0001$	
Canonical correlation	.47		.50		.78	
Explained variance	.22		.25		.61	
Group 1 centroid	.36		1.13		1.86	
Group 2 centroid	-.77		-.29		-.82	
Percent correct classification						
Overall	74		83		90	
Group 1	85		53		82	
Group 2	51		91		94	

^aIn group 1, 560 students tried, 260 did not (group 2).

^bIn group 1, 115 students were daily users, 455 were triers (group 2).

^cIn group 1, 115 students were daily users, 260 had never used (group 2).

115 males who reported daily use at initial assessment, 86 were reassessed at 6-month follow-up and 77 were reassessed at 12-month follow-up. For maintenance of a better subject-to-variable ratio in the discriminant analysis, the number of variables was reduced to seven. Several composite variables were formed by standardization of item values and summation of component items. Marijuana and alcohol use composites combined number of uses in the last week with daily use. A family smoking composite combined items on mother, father, sister, and brother smoking. A peer smoking composite included items on best friend smokes and the number of friends who smoke. A cigarette use in the last week composite combined cigarettes smoked yesterday and those in the last week. The remaining questionnaire items used in this analysis were the number of friends who use SLT, tried smoking, and had the intention to smoke.

The discriminant analysis of the 6-month follow-up data yielded a significant Wilks' λ of .85 ($P < .002$) that explained about 15% of the variance and classified 77% correctly. The structure coefficients indicated that the "friends

use of smokeless tobacco" was strongly related to continued daily use (.66) and peer smoking was negatively related (-.36). For the 12-month data, the Wilks' λ was .91, $P < .01$. Nine percent of the variance was explained, and 82% of the cases were correctly classified. Only the number of friends using SLT and the marijuana use composite were related to the function. Peer influence seems to be important in maintaining a pattern of daily SLT use.

Multiple Drug Use Among Male Adolescents

In an earlier study, we (5) found evidence of significant concurrent use of drugs among male adolescents and particularly among daily users of snuff and chewing tobacco. Among the male adolescents in this study, 10.5% reported smoking cigarettes in the last week, 14.4% indicated marijuana use in the last week, and 37.0% responded that they had consumed alcohol in the last week. Forty-five percent of the respondents reported using at least one of these four substances in the last week. Forty-seven percent of those reporting some use of these substances indicated that they used more than one. Among those who reported daily use

of SLT, 80.0% reported use of at least one additional substance. Specifically, use in the last week was reported by 20% for cigarettes, 35% for marijuana, and 73.9% for alcohol. The relationships between daily SLT use and any use of cigarettes, marijuana, and alcohol in the last week were examined by formation of 2×2 contingency tables and calculation of χ^2 and ϕ statistics. All three χ^2 were significant at the $P < .001$ level. The ϕ coefficients were: .13, .24, and .31 for cigarette, marijuana, and alcohol use, respectively. In addition, subject use of cigarettes, marijuana, and alcohol were significantly interrelated. The number of cigarettes in the last week was significantly correlated ($P < .001$) with the number of marijuana ($r = .48$) and alcohol ($r = .27$) uses in the last week. Similarly, use of marijuana in the last week was significantly related to alcohol consumption ($r = .49$).

Smokeless Tobacco Use As A Risk Factor For Other Drug Use

Male adolescents who report that they have used or tried SLT appear to be at increased risk to begin use of cigarettes, alcohol, and marijuana. Table 3 shows that SLT users who did not smoke at baseline were significantly more likely to report smoking at 1-year follow-up (5.8%) than those who did not use either substance at baseline (0.5%). Similarly, subjects who reported no use of alcohol in the last week at baseline were more likely to report use of alcohol at 1-year follow-up if they had reported use of SLT at initial assessment (29.0% vs. 11.6%). For marijuana, a significantly greater proportion of the baseline SLT users who had not reported use of marijuana at initial assessment reported it in the last week at 1-year follow-up (12.4% vs. 2.0%). The strength of the relationship between new use of cigarettes, alcohol, and marijuana at follow-up and having used SLT at baseline was indicated by ϕ coefficients of .13, .21, and .18, respectively.

Having used SLT was also related to increased use of cigarettes, alcohol, and marijuana at follow-up for all males, regardless of their previous status for these substances. Baseline SLT users were significantly more likely to have increased their use of cigarettes, alcohol, and marijuana at 1-year follow-up than were males who had not used snuff or chewing tobacco (table 3). For increased use of cigarettes, alcohol, and marijuana, the ϕ coefficients were .12, .15, and .20, respectively.

DISCUSSION

Although it may be true that the rate of cigarette smoking among adolescent females is higher than that of males, the findings of this study reveal that the combined use of cigarettes and SLT may be substantially higher for male adolescents. The extent to which these SLT users later take up cigarette smoking is a critical issue, and additional longitudinal studies are needed to examine it. This "gateway" transition from SLT use to cigarette smoking may be occurring with surprising regularity as adolescent males become older and face the possible social consequences of chewing tobacco and snuff use (e.g., dating-age females who do not find this behavior attractive). Given the increased restrictions on smoking in public places, the prevalence of the opposite transition (i.e., from cigarette smoking to SLT use) may be an issue of public concern as well.

The analysis of the concurrent data replicates findings of the earlier study (5). Both analyses indicate that peer use of SLT and experience with cigarette smoking were the primary discriminators between male adolescents who had tried snuff and chewing tobacco and those who had not. Similarly, results of both studies indicated that peer use of SLT discriminated between male daily users and those who had never tried it. This replication of the importance of peer use supports the adoption of social skill training to resist peer pressure as an effective intervention strategy. Although some differences did occur in secondary factors across grade level, the major discriminating factors appear to be consistent. The current study provides evidence that peer use of SLT is the primary factor distinguishing between male adolescents who have become daily users and those who have tried it but have not gone on to become daily users. It seems that peer influence is important not just at onset but in the development of a daily use pattern.

The prospective relationships to the onset of SLT use were relatively small. However, one interesting pattern that is consistent with a social pressure model did emerge in the 12-month follow-up analysis. Offers of alcohol, cigarettes, and marijuana were all significant predictors of the onset of SLT use. Additional research including the assessment of offers is needed if investigators are to examine more fully the role of social pressure in the onset process.

TABLE 3.—Percentage of male users and nonusers of SLT and other substances

SLT use at baseline	Use (last wk) at 1-yr follow-up, nonusers at baseline			Increased use (last wk) at 1-yr follow-up, all students		
	Cigarettes	Alcohol	Marijuana	Cigarettes	Alcohol	Marijuana
User, %	5.8	29.0	12.4	6.8	25.4	14.7
Nonuser, %	0.5	11.6	2.0	1.5	12.5	2.0
χ^2 ^a	8.3 ^b	16.2 ^c	16.0 ^d	7.07 ^b	13.1 ^c	21.7 ^d
ϕ coefficient	.13	.21	.18	.12	.15	.20

^aDegree of freedom = 1.

^b $P < .01$.

^c $P < .001$.

^d $P < .0001$.

It appears that once male adolescents establish a daily pattern of SLT use, most of them continue to use it daily. In this study, 76.6% of the daily users still reported daily use at 12-month follow-up. My associates and I (5) found 71% of the youths were still using it daily at a 9-month follow-up. How this pattern relates to the finding that only 30% of the daily cigarette smokers in this sample reported continued daily smoking at 12-month follow-up is not clear. One explanation is that the daily SLT users in this study may be more addicted than the daily smokers. Another is that a more consistent use pattern is possible for those who use snuff or chew tobacco because they can be used less obtrusively within school and home environments. In addition, social pressure from peers and adults to stop SLT use may be lessened. Clearly, replication by more direct measurement methods (e.g., self-monitoring and direct observation) are needed for careful and rigorous examination of the self-quitting process. Also examined in the current study were changes in habits among daily SLT users, and again, peer use was the best predictor of continued daily use at 6- and 12-month follow-up. This finding is consistent with a social influence model.

Parent and sibling use of SLT was not related to either the beginning or continuation of its use by the participants in this study or the previous one (5). This is an interesting finding because investigators (9-11) who conducted a number of prospective studies of adolescent smoking have also reported no relationships between these family modeling factors and adolescent smoking. Additional research specifically directed at the role of family members in the onset and maintenance of adolescent SLT use would help to clarify these relationships.

In both the current study and Ary et al. (5), tobacco, alcohol, and marijuana use appear common in adolescent males, with 42%-45% reporting use of at least one of these substances in the last week. Among those reporting some use, 43%-45% stated they had used more than one substance in the last week. Multiple substance use seems particularly high among daily SLT users, with 80%-83% reporting one or more other substances. In both studies, an unusually high percentage of daily SLT users indicated drinking alcohol in the last week (73%-74%). A closer examination of adolescent drug use patterns, with particular attention to the situations, antecedent events, and the consequences of use for each substance would be helpful in the development of efficacious interventions.

Data from this study support an earlier finding (5) that SLT use was identified as a risk factor for the use of other drugs. Those who use SLT were more likely to *begin* use of cigarettes, marijuana, and alcohol than were other subjects; having used SLT was related to *increased* use of cigarettes, marijuana, and alcohol among adolescent males. Although the consistency of these findings does not establish a causal relationship between SLT use and that of these other substances, it does point out the need for a more rigorous effort by researchers to examine these relationships. Longitudinal multimethod research might include in-depth interviews, direct observation, a series of telephone interviews over time to monitor change, and self-monitoring of use including corroboration by significant others.

The limitations of the current study should be noted. The "generalizability" of the findings may be restricted to this geographic region of the country. In addition, the conclusions are based on self-report questionnaire measures, the validity of which may be a concern, despite the inclusion of physiologic pipeline procedures. The "true" use rates for these substances may be a bit higher than reported here, due to the voluntary nature of student participation in the study. Although the decline rate was only 4%, those who did not participate may be more likely to use drugs (12). The implications of this type of bias on the generalizability of the correlational relationships explored here are not clear.

Future research efforts in this area might emphasize multimethod longitudinal research with special attention to the gateway transition process from use of SLT to that of cigarettes, marijuana, and alcohol. The development of effective prevention measures might include the integration of SLT components into existing school-based smoking prevention curricula (13), the involvement of dentists and physicians in office-based interventions, and the creation of cessation clinics modeled after those used with smoking cessation.

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Activity Involvement, Risk-taking, Demographic Variables, and Other Drug Use: Prediction of Trying Smokeless Tobacco¹

Steve Sussman,^{2, 3} Liana Holt,² Clyde W. Dent,^{2, 3} Brian R. Flay,⁴ John W. Graham,^{2, 3} William B. Hansen,^{2, 3} and C. Anderson Johnson^{2, 3}

ABSTRACT—Four activity participation variables (clubs, sports, church, and parties); two indices of "risk-taking" (preference for risk-taking, getting into trouble at school); three demographic variables (sex, ethnic group, socioeconomic status); and two drug use variables (trial of cigarettes and alcohol) were examined as correlates and prospective predictors of trial of smokeless tobacco in two cohorts of seventh graders in urban Los Angeles. The data were analyzed separately for males and females. Cross-sectional logistic regression analyses indicated that correlates of trying smokeless tobacco among the seventh-grade cohorts or among these same cohorts in the eighth grade (considering those persons who had not tried smokeless tobacco in seventh grade) generally included being white, trying cigarettes, risk-taking, and attending parties. Prospective logistic regression analyses with data from subjects who had not tried smokeless tobacco in the seventh grade indicated that predictors of subsequent trial of it generally included only being white and having tried cigarettes. Sports participation predicted onset only in one cohort of female subjects but not in males. Some activities that have been proposed as being predictive of smokeless tobacco use (e.g., sports participation) are generally irrelevant for a large sample of young adolescents in urban Los Angeles. White male cigarette smokers, regardless of the activities they have engaged in, are most likely to try smokeless tobacco.—NCI Monogr 8:57-62, 1989.

Involvement in relatively conventional activities (e.g., church, clubs, and sports) has been reported as less likely to be associated with drug use than involvement in relatively unstructured and less conventional activities, such as attending parties with peers (1, 2). Of course, activity participation may be differentially associated with various drugs. For example, Huba and associates (3) found a high association of party attendance and marijuana use, but only a slight association between party attendance and cigarette smoking and alcohol use, and no association between party attendance and heroin or hallucinogen use.

Chassin et al. (4, 5) suggested that use of SLT, because it receives relatively little social disapproval compared with

use of other drugs, is adopted by conventional adolescents (e.g., athletic, otherwise nondrug using) as one avenue of shared peer group experience. This suggestion is particularly interesting because other drugs, including cigarettes, tend to be used by risk-taking and rebellious youths (1). However, Dent and co-workers (6) found that being white, preferring to take risks, being male, and using cigarettes and alcohol were predictors for trying SLT 1 year later in a cohort of urban or suburban Los Angeles-based, young adolescents. They suggested that, aside from gender and ethnic variables, youths who use SLT are those who are willing or enticed to engage in a variety of other risk-taking activities consistent with Jessor and Jessor's (1) perspective on deviant-prone behavior.

Unfortunately, Dent et al. were unable to assess the relationship between conventional activities and trial of SLT. Anecdotal observations and a few rural studies suggest that its use is widespread among young male athletes (7, 8). Until recently, tobacco industry campaigns designed to change the visibility and social acceptance of SLT products among teenagers and young adults had been employing famous sports figures as actors, such as Bobby Murcer and Walt Garrison (9). Although television advertising of SLT has been curtailed (10), magazine advertisements are prevalent (e.g., in *TV Guide*), use on television at baseball games is noticeable (11), and manufacturers of beef jerky and bubble gum continue to offer their products packaged like snuff and chewing tobacco. Thus SLT may be used by youths who are actively engaged in school athletics. Of course, apparent relationships between participation in sports and use of snuff and chewing tobacco could have been due to a high rate of participation in sports by young males, rather than to a unique contribution of athletic participation to the prediction of trial of SLT. We (12) found that 80% of the seventh-grade males from a large sample of Los Angeles area schools report participation in sports activities, and we suggested that relationships between sports participation and SLT use are statistically redundant with gender.

Jones and Moberg (13) reported data that would seem to reconcile the results obtained by Dent et al. (6) with those of other researchers who found positive relationships between use of SLT and athletic team participation. In a large sample of seventh- through twelfth-grade students, they found that SLT users were more likely to report taking risks and were slightly more likely to be involved in team sports than nonusers. They examined use in males only, so that the relationships they obtained were not confounded by gender. Thus conventional activity participation by youths may not always be indicative of their being conservative in behavior, at least regarding participation in team sports.

ABBREVIATION: SLT = smokeless tobacco.

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²Institute for Health Promotion and Disease Prevention Research, 35 N. Lake Ave., Pasadena, California 91101. Address reprint requests to Steve Sussman, Ph.D.

³Division of Health Behavior, Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles, California 90024.

⁴Prevention Research Center, School of Public Health, University of Illinois, Chicago.

Unfortunately, their data are cross-sectional; in such studies, it is unclear whether psychosocial variables, e.g., risk-taking or sports participation, precede or are preceded by trial of SLT. Only longitudinal data can disclose a priori predictors of its use (14). A knowledge of a priori predictors of use is essential in the development of tobacco use prevention programming, which should be acquisition oriented (15). In addition, Jones and Moberg (13) examined only one activity, sports participation. An exploration of how use of SLT is related to several different activities would be informative.

Our present study served as a replication and extension of the study by Dent et al. (6). We examined concurrent and 1-year prospective relationships between trial of SLT and participation in club, party, sports, and church activities, as well as between trial use and risk-taking, demographic variables, and trial of cigarettes and alcohol in two samples of heterogeneous, young adolescents in urban Los Angeles.

METHODS

Subjects.—Subjects were from two cohorts of seventh-grade students. Cohort A consisted of 422 students from eight junior high schools in the Los Angeles metropolitan area. Cohort B consisted of 771 students from eight Los Angeles area schools, who were measured 1 year after cohort A (five of eight schools overlapped). Those schools were a random sample of 11 of 76 schools in the Los Angeles Unified School District, the school district of the City of Los Angeles and the largest in Los Angeles County. School participation was determined by district- and school-level agreement to participate in a longitudinal school-based study of drug use behavior, and all seventh graders were assessed in cooperating schools. In cohort A, 45% of the students were male, 46% were white, and 54% were nonwhite (i.e., 26% Hispanic, 19% black, and 9% Asian). In cohort B, 51% of the students were male, 49% were white, and 51% were nonwhite (i.e., 34% Hispanic, 12% black, and 5% Asian). Total attrition from cohorts A and B was 35% each and was due primarily to students transferring to nonparticipating schools. Trial of SLT, cigarettes, and alcohol by seventh-grade students did not differ between the full and the reduced longitudinal samples, which suggested that the sample was unbiased due to attrition.

Measures.—Students completed in-class, self-report questionnaires while in the seventh grade (May 1982 for cohort A, and May 1983 for cohort B) and 1 year later. On each testing occasion, students reported whether they had ever used cigarettes, SLT, or alcohol. To increase the validity of self-reports regarding tobacco products, we (16) collected saliva thiocyanate test samples. We scored drug use item responses as either dichotomous (SLT: never or one or more times) or trichotomous (cigarette smoking: never, once, or more than once; drinking alcohol: never, once, or more than once) to equalize cell size of response categories. Because of the greater use of SLT by whites than nonwhites in these samples and the desire for equal cell size, this predictor was dichotomized (whites vs. nonwhites).

Other questionnaire items included participation in four activities (clubs, parties, sports, and church); risk-taking and delinquent behavior (two indices, each composed of

four items); and three demographic variables (sex, ethnic group, and socioeconomic status). The club item requested the student to indicate the number of groups, such as Scouts, Young Men's Christian Association, or Boys or Girls Clubs, that he or she had been part of in the past 12 months. The party item requested that the number of parties be indicated that the student had attended with friends in the past 4 weeks. The sports item requested that the student indicate the number of times he or she played a competitive sport, e.g., baseball, swimming, basketball, or track in the last 7 days other than in a gymnastics class. The church item requested the student to indicate how often he or she attends services at a church, synagogue, mosque, or temple. These items were on 4- to 7-point rating scales.

The delinquent behavior items were on 4-point rating scales and included a student's being sent out of class for bad behavior, cheating on a test, being suspended from school, and destroying things on purpose that were not personal possessions. The risk-taking items included liking to take chances, thinking school was a waste of time, believing it was worth getting into trouble to have fun, and doing things the student is told not to do.

The test-retest reliability of all the above items ranged from 0.5 to 0.8, and the risk-taking and juvenile delinquency indices showed adequate discriminant and convergent validity (17, 18). Socioeconomic status was an 11-point rating-scale item that was derived from an open-ended response to a pretest item requesting the students to indicate their father's occupation and was scored on the basis of occupational status levels adapted from Hollingshead and Redlich (19).

Analysis: Prediction of trying smokeless tobacco.—The analysis strategy used involved the logistic multiple regression model (20) to predict a binary (0, 1) outcome variable that indicated initial trial of SLT. The model assumes that the probability of a student trying it is described by: $1/(1 + \exp(-\alpha - XB))$, where \exp indicates natural base exponentiation, α is an intercept (level) parameter, X is a vector of (given) predictor variables, and B is a vector of regression parameters to be estimated.

We tested two basic forms of this model: a cross-sectional form in which variables were used to predict previous trial of SLT and a prospective form in which variables were used to predict onset of its use 1 year later. The cross-sectional form allows identification of correlates of SLT trial, whereas the prospective/longitudinal form allows us to establish an order of precedence among activities or other possible predictors of SLT use (6, 14). Although causal inference should not be made, longitudinal analyses enable us to identify prospective factors that can identify youths at risk for beginning use of SLT.

We tested models in several subsamples. Gender differences exist in frequency of trying snuff and chewing tobacco (6); we postulated that a different model of onset may exist as well. Therefore, all analyses were done separately within male and female subsamples. Cohort subsamples were formed as a means of cross-validation. Similar results in both cohorts were taken as stronger indications of model effects compared with a single sample analysis. Because the cohorts were measured 1 year apart and shared only 50% of the same schools, replication of effects was of primary

interest (as opposed to some calculation of shrinkage). We also used grade level to define student subsamples when studying the cross-sectional form of the models. Prospective analyses include one sample of subjects at two grade levels. The cross-sectional analyses of seventh graders, which predicted their trial, included all students regardless of concurrent use (within each of the previously defined gender and cohort subsamples). All other analyses were performed in a subsample of students who reported that they had not used SLT at the time of their seventh-grade survey. In all, we tested the cross-sectional form of the model in eight subsamples (2 gender \times 2 cohorts \times 2 grades), and we tested the prospective form of the model in four subsamples (2 gender \times 2 cohorts).

Predictor variables were 10 of the measures described above: the four activities items, the two risk-taking indices, the two "other drug" use items, and two of the three demographic items (socioeconomic status and ethnicity).

Model parameter estimation was achieved by the LOGIT procedure in the SAS or Statistical Analysis System (21). In that program, the model likelihood ratio χ^2 reported is twice the difference in the log-likelihood between the tested model and a model with only intercept terms included (i.e., an omnibus test that no variables are significantly predictive). The interpretation of this χ^2 test is identical to likelihood ratio χ^2 tests performed in two-way contingency tables; i.e., large χ^2 values indicate rejection of the notion that the outcome and predictor variables are only randomly related. The program also computes a statistic labeled " R ," the square of which equals the percentage of the intercept-term-only (i.e., null) model log-likelihood accounted for by the predictors, analogous to R squared in ordinary least squares regressions. The R associated with individual variables (effect R) are related to the percent of log-likelihood reduction when that variable is included (given all other variables are included in the model). An effect R is analogous to a standardized regression coefficient in ordinary least squares regression.

RESULTS

Prevalence of Trying Smokeless Tobacco

Table 1 shows the prevalence of the two cohorts trying SLT at two times (seventh and eighth grade) by race and sex.

TABLE 1.—Prevalence of trying SLT by cohort, sex, ethnic group, and grade

Sex and ethnic group	No. of students		Grade 7		Grade 8	
	Cohort A	Cohort B	Cohort A, %	Cohort B, %	Cohort A, %	Cohort B, %
Females						
Asian	20	17	1	6	15	6
Black	49	49	4	12	6	12
Hispanic	50	130	2	8	2	8
White	108	179	8	11	19	15
All	227	375	6	10	12	11
Males						
Asian	21	21	5	14	10	19
Black	30	42	23	26	27	38
Hispanic	53	134	13	21	36	27
White	76	199	34	33	51	47
All	180	396	23	27	38	38

The results are similar to those found by Dent et al. (6). Males are approximately three times more likely than females to have tried SLT (23% vs. 6% and 27% vs. 10% in seventh-grade cohorts A and B, respectively; 38% vs. 12% and 38% vs. 11% in eighth-grade cohorts A and B, respectively). Whites generally report the highest percentage of trying SLT for males and females. Hispanics and blacks report the next highest percentage, followed by Asians.

Correlates of Trying Smokeless Tobacco: Cross-sectional Analyses

All model χ^2 were significant (tables 2 and 3).⁵ Results for seventh-grade females were similar across cohorts. Attendance at parties and, less consistently, getting into trouble at school and trying cigarettes were positively associated with trying SLT. For seventh-grade males, being white and trying cigarettes were associated with trying SLT across cohorts. Alcohol use by cohort A males was also significantly associated with their trying SLT.

Results for eighth-grade females were similar across cohorts. Being white and of lower socioeconomic status were associated with trying SLT across cohorts, and risk-taking and cigarette smoking were significant correlates as well in cohort B females. Risk-taking, cigarette smoking, and alcohol use for eighth-grade males were consistently associated with trying SLT; also, being white and attending parties were associated with its use in cohort A males, whereas participation in sports for cohort B males was marginally related ($P < .08$) to trying SLT.

Predictors of Trying Smokeless Tobacco: Prospective Analyses

All model χ^2 tests were significant (tables 2 and 3). Being white and having tried cigarettes in the seventh grade were the only consistent predictors of trying SLT by the eighth grade across gender and cohort (cigarette smoking was not a significant predictor, but alcohol use was a significant predictor among cohort A females). Sports participation was a significant predictor of beginning SLT use, and risk-

⁵All two-way interactions between ethnicity and the other nine predictor variables were examined. We used gender, cohort, and grade indicators to construct analysis subsamples, and therefore they were not included as statistical variables. No significant two-way interactions with ethnic group were found, and in the interest of parsimony, they are not included in tables 2 and 3.

TABLE 2.—Prediction of trying SLT by cohort A

Variable name	Seventh grade cross-sectional					Eighth grade cross-sectional					Seventh- to eighth-grade prospective				
	Females		Males			Females		Males			Females		Males		
	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect
Clubs	0.49	.48	0.00	0.01	.92	0.00	0.07	.79	0.00	0.29	.59	0.00	1.85	.17	0.00
Parties	7.47	.006	0.17	0.77	.38	0.00	1.14	.29	0.00	3.85	.05	0.07	0.69	.41	0.00
Sports	0.11	.74	0.00	0.67	.41	0.00	0.01	.91	0.00	0.99	.99	0.00	0.79	.37	0.00
Church	1.46	.23	0.00	0.15	.70	0.00	0.01	.94	0.00	0.01	.94	0.00	0.03	.87	0.00
Risk-taking	0.45	.50	0.00	2.10	.15	0.02	0.69	.41	0.00	6.72	.01	0.11	0.11	.74	0.00
School trouble	12.62	.0004	0.24	1.10	.29	0.00	0.11	.74	0.00	2.15	.14	0.02	0.00	.96	0.00
Socioeconomic status	0.06	.80	0.00	0.00	.99	0.00	3.34	.007	-0.09	0.02	.90	0.00	0.54	.46	0.00
Ethnic group	0.03	.87	0.00	7.18	.007	0.13	7.59	.006	0.17	13.37	.0003	0.18	4.85	.03	0.12
Cigarette use	2.44	.12	0.05	9.15	.003	0.15	1.72	.19	0.00	7.59	.006	0.12	1.24	.26	0.00
Alcohol use	0.31	.58	0.00	6.69	.010	0.12	0.66	.42	0.00	3.34	.07	0.06	7.35	.007	0.16
Model χ^2	53.11	.0001	0.35	52.22	.0001	0.35	20.57	.02	0.08	58.79	.0001	0.35	28.46	.002	0.19
(degrees of freedom = 10)													63.22	.0001	0.29

TABLE 3.—Prediction of trying SLT by cohort B

Variable name	Seventh grade cross-sectional					Eighth grade cross-sectional					Seventh- to eighth-grade prospective				
	Females		Males			Females		Males			Females		Males		
	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect	χ^2	P	Effect
Clubs	0.04	.84	0.00	1.26	.26	0.00	0.15	.70	0.00	0.51	.48	0.00	2.69	.10	-0.05
Parties	5.81	.02	0.12	2.91	.09	0.04	0.10	.75	0.00	0.64	.42	0.00	0.79	.37	0.00
Sports	0.84	.36	0.00	0.60	.44	0.00	1.23	.27	0.00	3.11	.08	0.05	4.26	.04	0.10
Church	2.01	.16	-0.01	0.38	.54	0.00	2.20	.14	0.03	0.56	.46	0.00	1.41	.23	0.00
Risk-taking	0.91	.34	0.00	2.49	.11	0.03	4.16	.04	0.09	3.44	.06	0.05	3.13	.08	0.07
School trouble	2.54	.11	0.04	2.47	.12	0.03	0.01	.94	0.00	0.05	.82	0.00	2.45	.12	0.04
Socioeconomic status	0.65	.42	0.00	0.10	.75	0.00	2.66	.10	-0.05	2.02	.15	-0.01	1.23	.27	0.00
Ethnic group	0.91	.34	0.00	11.69	.0006	0.13	4.79	.03	0.11	2.34	.13	0.03	5.73	.02	0.12
Cigarette use	13.29	.0003	0.20	36.85	.0001	0.24	9.71	.002	0.18	15.06	.0001	0.16	17.37	.0001	0.25
Alcohol use	0.07	.79	0.00	1.47	.23	0.00	1.41	.23	0.00	13.24	.0003	0.15	0.00	.98	0.00
Model χ^2	46.83	<.0001	0.29	78.80	.0001	0.32	46.05	.0001	0.34	66.18	.0001	0.33	50.18	.0001	0.35
(degrees of freedom = 10)													29.95	.0009	0.14

taking was a marginally significant predictor for females in cohort B. Seventeen percent (19 of 110) of the girls who reported participating in four or more competitive sports activities over the last 7 days reported having tried SLT, compared with only 8.5% (22 of 255) of them who reported participating in three or less competitive sports activities over the same time.

DISCUSSION

Our results suggest that the male youth who enjoys taking risks, smokes cigarettes, and drinks alcoholic beverages is the one who is most likely to have previously tried SLT by the eighth grade. Compared with females, males were three times more likely to try SLT. Most females may simply prefer not to use a substance that makes them spit. Possibly, prevention programs should include females in novel ways. The negative responses of females to the practices of chewing and dipping might be integrated into programs designed to build resistance to adoption of these behaviors (22). For example, female students in the classroom might give low popularity ratings for those types of males who use SLT and spit, indicate their unwillingness to be friends with users, and role-play their physical reactions to someone spitting as ways to deter use among males.

On the other hand, at least 8% of the females in each cohort reported having tried SLT by the seventh grade, which suggests that its use could become a problem drug for some females. As with the males, females who previously tried SLT tend to attend parties, smoke cigarettes, be white, and take risks. If these predictors were to operate as acquisition variables for males and females, other treatment implications might include teaching of alternative prosocial risk-taking activities (e.g., rock-climbing), self-management and coping skills, and self-confrontation skills, as well as needed education on the health consequences of SLT use (23).

In general, the prospective analyses indicated that being white and having tried cigarettes were predictive of onset of SLT use across gender. Participation in sports was a significant predictor of beginning use of it for females (but not for males) that gave some support to the suggestion that athletes are at higher risk for its use. This result must be interpreted with caution because it did not replicate across cohorts. In general, activity participation was not a significant predictor of SLT use. Also, we did not provide a strong replication of the findings by Dent et al. (6) that risk-taking predicted first use. In the present study, risk-taking and party attendance were significantly correlated ($P < .05$) with trial of SLT in the cross-sectional analyses only. Perhaps participation in activities and preference to take risks are not relevant to the initiation of SLT use, at least in student samples from primarily urban areas, although they are associated with previous trial of the substance. At a minimum, these variables are not directly predictive of trial of SLT. Although not measured herein, the perception of relative safety in the use of snuff and chewing tobacco (4, 5) could lead to the initiation of the substance by a wide variety of youths in several contexts.

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Initiation and Use of Smokeless Tobacco in Relation to Smoking¹

Arthur V. Peterson,^{2, 3} Patrick M. Marek,² and Sue L. Mann^{2, 4}

ABSTRACT—Questionnaire data obtained from 1,631 tenth grade students in 14 school districts in the State of Washington are used in this investigation of the relationship between the onset processes for smokeless tobacco use and smoking. Emphasized is the use of time-to-event data on the ages of occurrence of six events in these onset processes. Concepts and methods for the statistical analysis of time-to-event data are demonstrated. The occurrence of events in the smoking onset process are strongly related to increases in the subsequent onset rate for smokeless tobacco use. Compared with *before* initial smoking has occurred, the onset rates for weekly smokeless tobacco use *after* initial smoking has occurred are 2.03 ($P < .001$) and 6.72 ($P < .001$) times as large for males and females, respectively. Furthermore, both initial and weekly use of cigarettes contributes to the risk of subsequent weekly smokeless tobacco use. Conversely, the steps in the onset process of smokeless tobacco use are strongly related to increases in the subsequent smoking onset rate. Possible implications for intervention in prevention of smokeless tobacco use and for further research are discussed.—NCI Monogr 8:63-69, 1989.

The use of SLT among adolescents, especially snuff among adolescent males, has skyrocketed in recent years (1). This development has ominous health implications, because SLT contains known carcinogens and because a growing body of epidemiologic evidence indicates that its use carries the risk of various adverse health effects including oral cancer (2). Scientists are expending considerable effort to establish the circumstances and factors related to SLT use and its onset process among youth and to incorporate these findings in the designs of effective prevention programs.

Determining the relationship between smoking and the use of SLT is important for their investigation of 1) smoking as a possible risk factor for the onset of SLT use and 2) the extent to which such use is associated with subse-

quent smoking. That both cigarettes and SLT are tobacco products and contain absorbable nicotine indicates strongly that an associated nicotine dependence may result in individuals taking up one when quitting the other to maintain a habituated nicotine level.

It is clear that the concurrent use of cigarettes and SLT are associated (3-6). The purpose of our investigation is to use data on the ages at which young people begin to smoke and use SLT to examine the relationship between the smoking and SLT onset processes. Some basic concepts and methods for the statistical analysis of time-to-event data are demonstrated.

The concept of a smoking onset process, i.e., a series of events that describe an increasing level and/or frequency of cigarette use, has been advanced by Flay et al. (7), Leventhal and Cleary (8), Hirschman and co-workers (9), and others. Our description of such a process consists of 1) specifying meaningful events of tobacco use and 2) determining transition rates between the events with data on the times (ages) at which the events occur. The investigations reported here are restricted to such events; other important aspects of the smoking onset process, such as social influences, the environment, and motivation, will be added in subsequent investigations. We used data on the ages of occurrence of six tobacco use events: initial, tenth, and first weekly use of SLT, and initial, tenth, and first weekly use of cigarettes.

METHODS

Survey procedures.—Tobacco use, including cigarette smoking and SLT, was assessed through a questionnaire administered in the classroom to entire grades of tenth-grade students in 14 rural and suburban school districts in the State of Washington in January 1986. Through an informational letter to parents and by in-class procedures, parents and students were fully informed in advance and were given an opportunity to ask questions and to decline to participate.

The tobacco survey was part of a baseline assessment of tobacco use among students in school districts participating with the Fred Hutchinson Cancer Research Center in the Hutchinson Smoking Prevention Project, a long-term, randomized controlled trial in school-based smoking prevention.

Of the total enrollment of 2,214 tenth graders, 1,918 (87%) took part in the survey. Twelve percent were absent from class; 0.2% (parents) and 0.8% (students) declined participation. Data for all questionnaire items pertinent in this investigation are available on 1,631 students. All results reported below are based on analyses of data from 1,631 students (840 males, 791 females).

ABBREVIATION: SLT = smokeless tobacco.

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²Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1124 Columbia St., Seattle, Washington 98104. Address reprint requests to Arthur V. Peterson, Ph.D., Cancer Prevention Research Program MP603.

³Department of Biostatistics, University of Washington, Seattle.

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Measures we used to enhance the accuracy of the responses to the questionnaire items included 1) administration of the questionnaire on an unannounced date; 2) procedures to maintain confidentiality and assurances about these to the parents and students; 3) classroom procedures designed to maintain and demonstrate confidentiality, including the use of study identification numbers and the handling of questionnaires by project data collectors only; 4) explanation and collection of saliva samples from all participating students concurrent with administration of the questionnaire; and 5) explanation of the data collection objectives and the important role of the students in achieving them.

The questionnaire included items that assessed various aspects of current, past, and future intended use of cigarettes and SLT products. The wording for questions and multiple-choice responses for cigarettes was similar to that for SLT, so that differences in patterns for smoking and SLT use could be ascertained without confounding from differences in the nature or wording of the items.

Analysis.—For binary data items (e.g., whether a certain level of past or current use of tobacco was achieved), simple proportions (prevalences) are reported. Data on time-to-smoking and time-to-SLT-use are analyzed by standard time-to-event statistical methods (survival analysis methods) that accommodate data on individuals for which the event (smoking, SLT use) has not occurred (censoring). Two time-to-event statistical methods are used:

- 1) Kaplan-Meier survival curves provide a descriptive display of time-to-event data (e.g., age at initial smoking) obtained on a set of individuals. When data on time-to-event are completely available for all participants, then this curve (at any age t) is simply the fraction of individuals whose observed times-to-event are greater than t (e.g., a fraction of individuals who have not smoked at age t). The Kaplan-Meier curve can also accommodate the situation characteristic of time-to-event data, when, for some individuals, the age at initial smoking is not known, but only that no smoking has occurred by a certain age (e.g., the age at which data collection occurs). Mathews and Farewell (10), Lawless (11), Miller (12), and Kalbfleisch and Prentice (13) provide further descriptions of the Kaplan-Meier survival curve, including formulas for its computation and assumptions for its use.
- 2) We used the Cox regression method (10-14) to analyze the impact of the occurrence of one tobacco use event (e.g., initial smoking) on the subsequent rate of onset of another event (e.g., weekly use of SLT). By such analyses, one can investigate directly the interrelationship between the smoking and SLT use onset processes. The Cox regression method models the onset rate $\lambda(t)$ for some specified event (e.g., weekly use of SLT) as a function of the follow-up time t (e.g., age). The model specifies that the onset rate $\lambda(t; z)$ for any individual with explanatory (regression) variables z_1, z_2, \dots, z_p is just the product of a "baseline" onset rate $\lambda_0(t)$ and a

function $g(z; \beta)$ of the covariates, often taken to be the exponential function $g(z; \beta) = \exp(z; \beta)$:

$$\lambda(t; z) = \lambda_0(t) \cdot \exp(z; \beta),$$

where $\lambda_0(t) > 0$ is a completely unspecified baseline onset rate, $z = (z_1, \dots, z_p)$ is a regression vector consisting of the p explanatory variables, and $\beta' = (\beta_1, \dots, \beta_p)$ is a vector of regression coefficients to be estimated from the data.

The Cox regression model offers a number of desirable features and improvements over more traditional methods that make it particularly helpful in investigations of onset processes, such as those of smoking and SLT use:

- 1) The age-specific onset rate $\lambda(t)$, a meaningful measure of smoking onset as a function of age, is modeled directly.
- 2) No assumption is made about the shape or magnitude of the onset rate as a function of age. It is data determined.
- 3) The quantities $\exp(\beta_1), \dots$, for which estimates are readily obtained by the usual partial likelihood analysis, have the useful interpretation of *relative onset rates*, e.g., the estimated smoking onset rate for prior SLT users relative to that for prior nonusers.
- 4) As in other regression models, the effect of other variables can be conveniently controlled by their inclusion as covariates in the regression model.
- 5) Unlike binary data methods, the model and analysis can accommodate censored data.
- 6) The model can be generalized in numerous ways for adaptation to a wide range of applications.

Used in this paper is a generalization that allows an explanatory variable to depend on follow-up time t . In our application below, we let $z_1 = z_1(t)$ depend on the follow-up time (age) and define it to be the indicator function for the occurrence of a specified prior event (e.g., the occurrence of initial smoking), taking the value 0 before the event occurs and 1 afterward. The quantity $\exp(\beta_1)$ is interpreted as the relative onset rate (e.g., of weekly SLT use after the prior event of initial smoking compared with before). See the references above for a complete description of this model, its generalizations and assumptions, and method of analysis.

RESULTS

Prevalence of Smoking and Smokeless Tobacco Use

Table 1 presents, first for cigarettes and then for SLT, the fraction of boys and girls who have ever used, currently use, and have attained certain events of the onset process.

The percentage of males who have ever smoked cigarettes is about the same as have ever used SLT. More boys have dipped more than five pieces of SLT than have smoked more than five cigarettes (40.6% vs. 32.5%). Almost 70% of the females have ever smoked cigarettes and about 31% have ever used SLT; almost 6% of the girls have used more than five pieces of SLT.

More boys are currently using SLT than cigarettes: 17.7% versus 14.4% (weekly use). Although 19.4% of the girls

TABLE 1.—Current use, lifetime use, and attainment of onset events: cigarettes and SLT

Use/onset/transition	Boys, %		Girls, %	
	Cigarettes	SLT	Cigarettes	SLT
Lifetime use				
Ever	69.8	71.1	68.6	31.2
>Five times	32.5	40.6	39.1	5.9
Current use				
≥Once/mo	19.7	25.3	26.1	2.8
≥Once/wk	14.4	17.7	19.4	1.4
Onset of use				
First	69.8	71.1	68.6	31.2
Tenth	30.8	40.5	37.7	5.8
First weekly	22.4	31.1	31.2	4.4
Transition probabilities				
Between no use and first	69.8	71.1	68.6	31.2
Between first and tenth use	44.1	57.0	55.0	18.6
Between tenth and weekly use	70.3	73.6	79.9	69.8

smoke cigarettes at least weekly, only 1.4% of them use SLT at least weekly.

Consistent with the results just presented, more boys attained the tenth use for SLT than for cigarettes (40.5% vs. 30.8%), and more boys attained weekly use of SLT than cigarettes (31.1% vs. 22.4%). Also, far fewer girls attained both tenth and weekly use of SLT than for cigarettes. It is noteworthy that 4.4% of the girls did use SLT weekly at one time in their lives.

Because tobacco use onset is a process of increasing use, presentation of the results in transition probabilities (lower portion of table 1) from one event to another is helpful. These results reinforce the ideas that 1) the higher

prevalence for male use of SLT compared with smoking is attributed mostly to the higher first-to-tenth use transition probability (57.0% vs. 44.1%), and 2) the drastically lower prevalence for female use of SLT compared with smoking is attributed to both a lower prevalence of initial use and a lower first-to-tenth use transition probability.

The extent to which cigarettes and SLT are used separately and concurrently is shown in table 2. Consistent with results from other studies, a strong relationship is evident between smoking and SLT use, for both lifetime and current use. First, a majority of males (60.2%) have used both cigarettes and SLT. Only about 1 of 3 males who have never tried SLT have tried cigarettes; 6 of 7 males who have tried SLT have also tried cigarettes. Fewer than 1 of 10 males who do not use SLT weekly smoke weekly, but more than 1 of 3 males who use SLT weekly also smoke weekly. Of the 25.5% of the boys who use tobacco at least once a week, 7.6% use cigarettes only, 11.7% use SLT only, and 6.2% use both.

Among females, 29.5% have used both cigarettes and SLT. Over 50% of the females who have never tried SLT use cigarettes, but more than 9 of 10 who have tried SLT have also tried cigarettes. On average, fewer than 1 in 5 girls who do not use SLT weekly smoke weekly, but more than 1 of 2 who are weekly SLT users smoke weekly.

Onset of Smoking and Smokeless Tobacco Use

The results presented to this point have described prevalence of current use, lifetime use, and the frequency of occurrence of certain onset events for smoking and SLT separately and together. These results have described the extent to which various smoking events occurred but not at what ages they occurred. Attention is now focused on the ages at which the onset events occurred, with emphasis on a description of the age-specific onset rates for first, tenth, and first weekly use for smoking and SLT. First, smoking and

TABLE 2.—Relationship between smoking and SLT use, %

Sex	Use/onset	Cigarettes only	SLT only	Cigarettes and SLT	Neither
Males	Lifetime use				
	Ever	9.5	10.8	60.2	19.4
	>Five times	10.2	18.4	22.3	49.3
	Current use				
	≥Once/mo	7.8	14.6	11.1	66.5
	≥Once/wk	7.6	11.7	6.2	74.5
	Onset of use				
	First	9.6	10.7	60.5	19.2
	Tenth	9.4	19.0	21.4	50.1
Females	First weekly	9.0	17.7	13.3	59.9
	Lifetime use				
	Ever	39.1	1.6	29.6	29.7
	>Five times	33.7	0.6	5.3	60.4
	Current use				
	≥Once/mo	24.0	0.8	2.0	73.3
	≥Once/wk	18.5	0.8	0.7	80.1
	Onset events of use				
	First	38.9	1.6	29.8	29.6
	Tenth	32.4	0.5	5.3	61.8
	First weekly	27.7	0.9	3.5	67.9

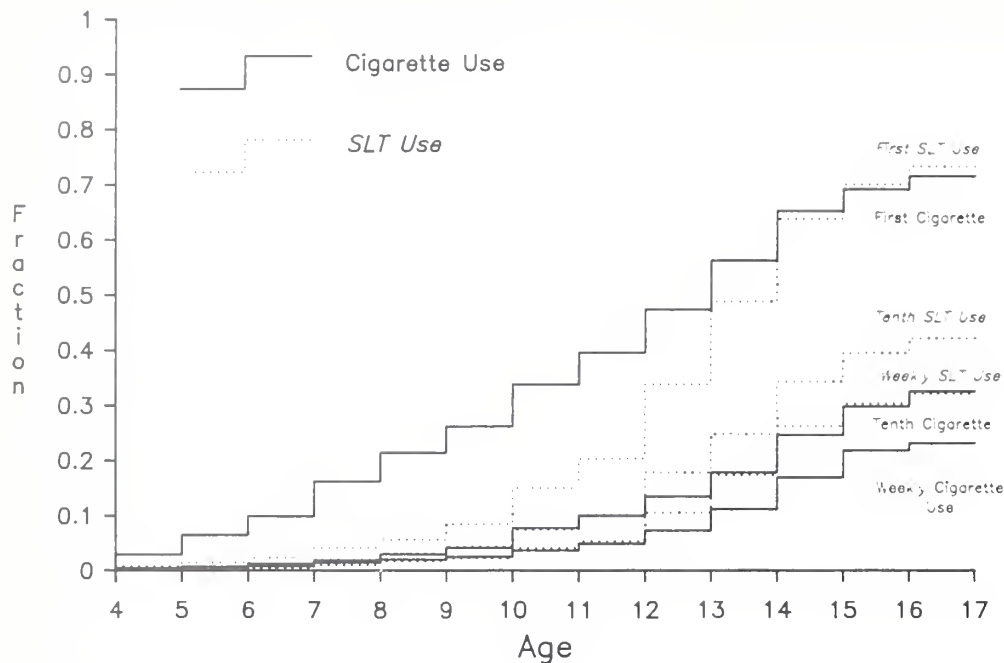


FIGURE 1.—Onset curves for smoking and SLT for 840 adolescent males.

SLT are considered separately and then together. We used basic methods of presenting and analyzing time-to-event data. The onset curves for first, tenth, and weekly use for cigarettes and SLT are shown in figures 1 and 2 for males and females, respectively. The onset curves indicate that the rates are greatest (onset curves increase the fastest) during certain age ranges shown in table 3.

It is clear that substantial differences exist between the age ranges when smoking and SLT onset occur. For males and females, initial SLT use occurred later than initial smoking. For males, tenth and weekly SLT use did not occur later than tenth and weekly use of cigarettes. Rather,

the onset rates were similar until the boys were 11 years old, after which more boys achieved tenth and weekly SLT use than tenth and weekly smoking. For females, tenth and weekly SLT use occurred later than tenth and weekly use of cigarettes.

Relationship Between Smoking Onset and Onset of Smokeless Tobacco Use

The relationship between the onset of smoking and that of SLT use in adolescents was investigated by a number of methods.

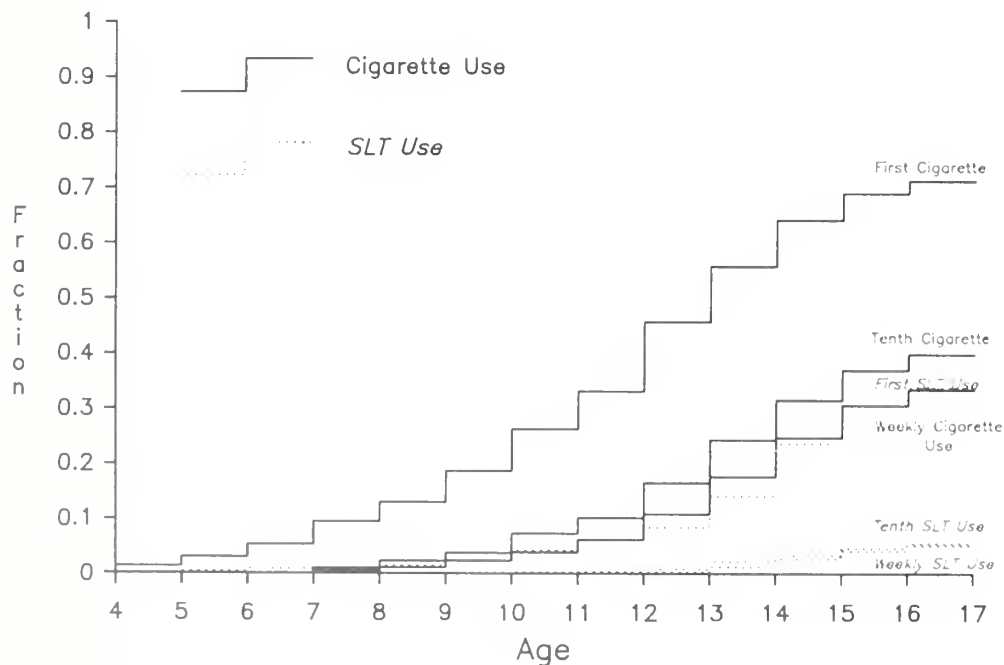


FIGURE 2.—Onset curves for smoking and SLT for 791 adolescent females.

TABLE 3.—Age ranges for high onset rates

Sex	Use					
	First		Tenth		First regular	
	Age range, yr	Percent onset ^a	Age range, yr	Percent onset ^a	Age range, yr	Percent onset ^a
Males						
Smoking	6-14	55	9-15	26	11-15	14
SLT	9-14	55	11-15	30	11-15	25
Females						
Smoking	8-14	51	9-15	33	10-15	27
SLT	12-16	26	11-15	5	12-16	5

^a Percent onset is for age range indicated.

First, joint distributions were computed for the age of occurrence of an event in the smoking onset process and that of the corresponding event in the SLT onset process. Time-to-event censoring was handled by inclusion of a "never started" category. From the joint distributions (not shown) of: 1) age at first use of cigarettes and at first use of SLT, 2) age at tenth use of cigarettes and age at tenth use of SLT, and 3) age at regular use of cigarettes and at regular use of SLT, a number of conclusions can be obtained.

One summary point of the joint distribution of ages of initiation of smoking and SLT use is the extent to which the smoking event occurs before the SLT use event, and vice versa, among those experiencing both smoking and SLT use events. As shown in table 4, smoking and SLT each occurred first in a substantial number of males. Among boys who used both, 25% tried SLT first and 60% tried cigarettes first. Fifteen percent first tried both at the same age. In contrast, the vast majority of females tried cigarettes first (76%) rather than SLT first (12.5%).

Finally, the following question is addressed: How are the age-specific onset rates for regular smoking related to the prior occurrence of steps in the SLT onset process for the 840 boys and 791 girls? Conversely, how are the onset rates for regular SLT use related to the prior occurrence of steps in the smoking onset process for both sexes? We investigated these questions using time-to-event regression methods developed by Cox (14). Data for all participants are included in these analyses; those not experiencing the end point of interest (e.g., weekly smoking, in table 5) are treated as censored.

The occurrences of steps in the SLT onset process are strongly related to increases in subsequent onset rate for

weekly smoking. From runs (i.e., individual analyses) 1 and 4 of table 5, the weekly smoking onset rate is 1.65 ($P = .002$) and 2.13 ($P < .001$) times as large for males and females, respectively, after initial SLT use has occurred compared with before initial SLT use. From runs 2 and 5, the weekly smoking onset rate is 1.83 ($P = .002$) and 3.25 ($P = .021$) times as large for males and females, respectively, after weekly SLT use began compared with before weekly SLT use.

Furthermore, evidence suggests that *each* of the SLT steps, initial and weekly use, contributes to the risk of subsequent weekly smoking. When both steps are included in the analyses for males (run 3), the occurrence of initial SLT multiplies the risk of smoking onset by 1.45 ($P = .047$), and the subsequent occurrence of weekly SLT use multiplies the risk of smoking onset by an additional 1.47 ($P = .08$) for a net multiple (1.47×1.45) of 2.13 times the smoking onset rate when no SLT event has occurred. For females (run 6), the relative risks are 2.04 ($P < .001$) and 1.80 ($P = .27$); not enough females use SLT regularly to provide the data needed in this data set for us to determine whether weekly SLT use provides an added risk of weekly smoking beyond the risk provided by initial SLT use.

The results for the converse relationship are similar (table 6). The occurrences of steps in the smoking onset process are strongly related to increases in the subsequent onset rate for SLT use. From runs 1 and 4 of table 6, the onset rate

TABLE 5.—Results of relative risk regression analyses of relationship of steps in onset process of SLT with onset of weekly smoking^a

Run	Relative rate and 95% confidence interval of weekly smoking onset ^b			
	After initial SLT use	P	After weekly SLT use	P
Males				
1	1.65 (1.20, 2.29)	.002	—	—
2	—	—	1.83 (1.24, 2.69)	.002
3	1.45 (1.00, 2.09)	.047	1.47 (0.95, 2.27)	.08
Females				
4	2.13 (1.50, 3.02)	<.001	—	—
5	—	—	3.25 (1.20, 8.81)	.021
6	2.04 (1.42, 2.93)	<.001	1.80 (0.64, 5.07)	.27

^a Analyses used data on 840 males and 791 females, of whom 188 and 247, respectively, attained weekly smoking.

^b Values in parentheses represent 95% confidence intervals.

TABLE 4.—Precedence of smoking vs. SLT among individuals using both, %

Use	Smoking event occurred first	SLT use occurred first	Simultaneous occurrence
Males			
First	60.0	24.9	15.1
Tenth	44.2	28.2	27.6
Weekly	43.4	31.0	25.6
Females			
First	76.3	12.5	11.2
Tenth	73.8	11.9	14.3
Weekly	60.7	14.3	25.0

TABLE 6.—Relative risk regression analyses of relationship of steps in onset process of smoking with onset of weekly SLT use^a

Run	Relative rate and 95% confidence interval of weekly SLT use ^b			
	After initial smoking	P	After weekly smoking	P
Males				
1	2.03 (1.56, 2.62)	<.001	—	
2	—		3.50 (2.55, 4.82)	<.001
3	1.65 (1.25, 2.18)	<.001	2.74 (1.95, 3.85)	<.001
Females				
4	6.72 (2.34, 11.92)	<.001	—	
5	—		4.57 (2.31, 9.06)	<.001
6	4.56 (1.49, 14.0)	<.001	2.63 (1.29, 5.40)	<.001

^a Analyses used data on 840 boys and 261 events and 791 girls with 35 events.

^b See table 5, footnote b.

for weekly SLT use is 2.03 ($P < .001$) and 6.72 ($P < .001$) times as large for males and females, respectively, after initial smoking has occurred than that before it occurred. This result for females is particularly striking: Females who have tried cigarettes are at almost seven times the risk for using SLT as those who have not. From runs 2 and 5, the onset rate for weekly SLT use is 3.50 ($P < .001$) and 4.57 ($P < .001$) times as large for males and females, respectively, after weekly smoking than before it occurred. Furthermore, evidence is clear that *each* of the smoking onset steps, initial and weekly use, contributes to the risk of subsequent weekly SLT use. When both steps are included in the analysis for males (run 3), the occurrence of initial smoking multiplies the risk of onset of weekly SLT use by 1.65 ($P < .001$), and the (subsequent) occurrence of weekly smoking multiplies the risk of onset of weekly SLT use by an additional 2.74 ($P < .001$), for a net multiple (1.65×2.74) of 4.5 times the SLT onset rate when no smoking event has occurred. The corresponding multiples for females (run 6) are 4.56 ($P < .001$), 2.631 ($P < .001$), and 12.0 (4.56×2.63).

DISCUSSION AND CONCLUSION

A consistently strong relationship is observed between the onset processes of SLT and smoking among adolescents. In particular, the occurrence of events in the smoking onset process is strongly related to increases in the subsequent onset rate for SLT use. Conversely, the occurrence of steps in the onset process of SLT use is strongly related to increases in the onset rate of subsequent smoking.

The finding that prior use of SLT is a risk factor for smoking indicates that prevention of its use may also help prevent smoking. Conversely, the finding that prior smoking is a risk factor for SLT use indicates that prevention of smoking may also help prevent SLT use. These results indicate the possible desirability of combining the prevention components of both within an overall intervention program. Such integration also makes practical sense in light of the tobacco common denominator between smoking and SLT use and the needs of schools for integrated interventions.

Several limitations of this investigation should be noted. The data used in these analyses on the onset processes for smoking and SLT use are recall data collected retrospec-

tively from a cross-sectional survey. Resulting limitations include: 1) Recall bias may be present because the data are limited to those individuals who can remember, and the recall may be biased among those who remember. 2) The sample does not correspond to a defined cohort but is a modification (by in- and out-migration) of some identifiable original cohort. However, to the extent that in- and out-migrating students are similar in their SLT and smoking onset patterns, no bias would result.

Also, these data on occurrence of events in the smoking and SLT onset processes span a period (1975–1985) during which the prevalence of SLT use was increasing rapidly. As a result, the relationship between the onset of both during such a period necessarily includes the effects of temporal changes in prevalence.

These investigations illustrate how survival analysis methods, and in particular survival analysis regression methods, can help to provide insight into the onset of individual steps of the smoking onset process, the relationship between age and the onset rate of various tobacco use events, and the degree to which onset of different events are related. Results of such investigations can contribute to the design of health-promoting interventions by guiding the choice of component, delivery method, and age and grade at which they are provided.

Further research is indicated in several directions: how the effect of SLT use on subsequent smoking onset depends on age and inclusion of other aspects of the tobacco use onset processes including social, environmental, and motivation variables. Finally, cohort studies are needed.

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Prevalence and Predictors of Smokeless Tobacco Use: Iowa's Program Against Smoking¹

Julie A. Burke,² Rebecca Arbogast,² Samuel L. Becker,² Michelle Naughton,³ and Ronald M. Lauer^{4, 5}

ABSTRACT—Data from surveys of adolescents were analyzed so that we could determine the prevalence of smokeless tobacco use and identify and compare the concurrent correlates of its use and cigarette smoking. Panel data from seventh through eleventh and eighth through twelfth graders between 1980 and 1984 and cross-sectional data from seventh graders in 1980 and 1985 suggest that boys are more likely to use SLT than are girls and that the boys' use has increased with age and over time. Concurrent correlates of seventh-grade boys' and girls' SLT use and cigarette smoking were identified with discriminant analyses. Predictors of smokeless tobacco use were compared with those of weekly smoking for boys and girls separately. Predictors of use by boys were also compared with those by girls. Trying alcohol and the other form of tobacco were the only predictors that related to the use of either form by boys and girls. Differences among other predictors were noted and their implications for prevention are discussed.—NCI Monogr 8:71-77, 1989.

Following decades of decline, the sale of SLT has increased steadily since 1970 (1). This increase and the mounting evidence of deleterious health consequences from its use (1, 2) have prompted interest in the demographic and psychosocial characteristics of those responsible for recent increases in consumption.

Although SLT use by adults has remained relatively constant at 3%-4% for males and 1% for females (1), that for adolescent males, however, has emerged (in a recent national survey) as representative of a group whose SLT use is increasing. According to the 1985 National Institute on Drug Abuse Household Survey, 16% of the males under 21 years of age had used SLT within the preceding year and 10% were using it at least once a week (1). Increased use by adolescent males is confirmed by cross-sectional data from several recent regional surveys (1-19) as well as longitudinal data from the Bogalusa Heart Study (20, 21). Taken collectively, these data show that SLT use among adolescent males 1) is more prevalent than among females, 2) is increasing with age, and 3) is increasing over time.

In this paper, we provide additional information on the prevalence of SLT use among adolescents and report our

initial efforts to identify demographic and psychosocial correlates of such use. Because a recent study (17) reported that some of the social factors influencing adolescent smoking were also related to the use of SLT, our examination of its correlates concentrated on variables theoretically and empirically linked to adolescent smoking.

The role of social institutions and relationships in constraining deviant behavior, such as smoking, is emphasized by the social bonding theory (22). In studies of adolescent smoking based on this theory, researchers found that adolescents were more likely to smoke if they experienced problems in relationships with parents or peers; were less committed to, or successful in, conventional arenas such as school or church; or were less committed to conventional systems of beliefs (23-28). On the basis of this work, we chose to examine the influence on SLT use of variables assessing attachment to parents and peers, commitment to and success in school, adherence to a religion or faith, and commitment to conventional values. Because advocates of several theories (e.g., those on social learning and differential association) argue that adolescents' smoking is influenced by the smoking of significant others (25-28), we assessed the smoking behavior of parents, siblings, and friends. We also examined the relationship between SLT use and demographic variables such as sex, age, and head of household's occupation.

METHODS

Population and procedures.—We drew on survey data from two research projects. In the Muscatine Smoking Study, researchers designed a questionnaire to assess tobacco use that was administered annually between 1980 and 1984 in two middle schools and one high school in Muscatine, Iowa. Public school students in grades 7 through 12 were surveyed in the first 4 years of the study and grades 9 through 12 in the final year. Less than 9% of the sample was nonwhite. Longitudinal data were available from 443 students who were surveyed all 5 years of this project. Data from 427 seventh graders surveyed in 1980 are also reported.

Additional data are presented from the first year of the Three Community Smoking Prevention Project. All seventh-grade students in three demographically comparable Iowa communities were surveyed twice during the 1984-1985 school year. In the fall, 1,207 students and in the spring 1,170 were surveyed. Analyses were performed on the data from 1,064 students who were surveyed in both waves. Reflecting their home communities of Burlington, Clinton, and Muscatine, these students were predominantly white and from middle- or working-class families.

ABBREVIATION: SLT = smokeless tobacco.

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²Department of Communication Studies, University of Iowa, 105CSB, Iowa City, Iowa 52242. Address reprint requests to Julie A. Burke, Ph.D.

³Sociology Department, University of Iowa.

⁴Department of Pediatrics, University of Iowa Hospitals and Clinics.

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Measures.—Several questions elicited information on tobacco use; one was about the frequency of SLT use, and three were on smoking. Respondents were asked about the frequency and quantity of their smoking. They were also asked to place themselves in one of five categories along a continuum from nonsmoker to heavy smoker.

No biochemical measure validated self-reported SLT use. Saliva samples collected and tested for thiocyanate, a compound found in higher concentrations in the saliva of regular smokers, validated self-reported smoking. Mean salivary thiocyanate levels, compared across smoking groups, indicated that confidence in the self-report measures was warranted. For a discussion of the use of such group comparisons for validating self-reports, *see* Akers et al. (29).

To determine whether adolescents experience problems in their social relationships, we assessed attachment to family, peers, and community with items used in previous research. An attachment-to-mother index measures the frequency with which respondents' mothers understand them, praise them, talk with them about their plans and problems, make them feel close, behave in a way they admire, and seem willing to listen ($\alpha = .89$). An attachment-to-father index is made up of the same six items but with the father as the referent ($\alpha = .92$). An attachment-to-friends index measures the frequency with which respondents' friends understand them, praise them, talk about their thoughts and feelings, make them feel close, behave in a way they admire, and do things that make them happy ($\alpha = .86$). A single item measured attachment to hometown.

We also assessed several variables related to commitment to and success in school with questions asked in previous research. Single items measured educational aspirations, amount of time spent on homework, self-reported grade-point average, and concern about teachers' appraisal of them. A school trouble index assessed the extent to which students have problems adjusting to the school environment, as indicated by their agreement with three items: People at school blame my group if there is trouble, people at school think of me as a troublemaker, and I would like to quit school ($\alpha = .69$). We constructed an index to measure social integration and success in school that asked respondents whether they perceive themselves as being leaders, having friends who are active in school activities, being popular, and being in the "top crowd" ($\alpha = .73$).

Because religion represents another arena in which adolescents may learn conventional values, we also assessed religiousness. A single item asked respondents how closely they adhered to religious precepts.

To determine adolescents' commitment to conventional values, we assessed their beliefs about obedience to authority. Respondents were asked to indicate the extent of their agreement with the following statements: We all have a moral duty to obey the law, the fact that it is against the law makes the use of drugs wrong, the rules or moral beliefs that my parents have are good enough for me. These items have also been used in previous research based on the social bonding theory.

We measured the smoking behavior of several significant others: mother, father, sister, brother, best female friend, and

best male friend with five-point scales ranging from never to every day.

We assessed demographic variables including age and sex. Using the 1970 detailed occupation codes of the Census Bureau, we also classified head of household's occupation to obtain a rough approximation of occupational prestige.

Because trying other illicit substances has been related to the likelihood of smoking, we also assessed the frequency of alcohol consumption. Finally, we explored whether several beliefs about the consequences of smoking might make SLT a more attractive alternative. We asked respondents whether they associated smoking with the following consequences: hurting sports ability, endangering health, and leaving a bad smell on breath and clothing.

RESULTS

Prevalence of Tobacco Use

The panel data allowed us to assess trends among adolescents as they matured. Table 1 reports the SLT use of two cohorts of boys and girls over a 5-year period as they progressed from seventh through eleventh or eighth through twelfth grade.

In this panel, for all grades and years, boys were substantially more likely than girls to use SLT. Most of the SLT use among girls was occasional rather than weekly or daily. For boys, the pattern was one of steadily increasing use. Only 16% of the younger and 21% of the older cohort had tried SLT at least once in 1980, but its use increased annually for both cohorts; by 1984, 46% of the younger and 57% of the older cohort had tried it at least once. The proportion of boys who had tried SLT was larger for the older than for the younger cohort for each year between 1980 and 1984.

A comparison of cross-sectional data from Muscatine seventh graders also revealed dramatic increases across time in boys' use of SLT (table 2). In 1980, 18% of the Muscatine seventh-grade boys and 1.5% of the girls had tried SLT; in 1985, 59% of these boys and 18% of the girls reported having tried it. For boys, both occasional and regular use of SLT increased substantially between 1980 and 1985; occasional use was responsible for girls' increased use.

Parallel data for smoking indicated that experimentation with cigarettes also increased for boys and girls between 1980 and 1985. However, during this period, we found a decline in weekly use of cigarettes by boys.

Concurrent Predictors of Tobacco Use

Although the data from seventh graders in the 1984–1985 wave of the Three Community Smoking Prevention Project revealed that some individuals used both forms of tobacco, the overlap between groups was not substantial. In the overall sample, 39.5% had neither smoked cigarettes nor tried SLT, and only 3.9% of the individuals had tried SLT at least once *and* smoked an average of one cigarette a week.

We ran several stepwise discriminant analyses to identify the predictors of SLT use and cigarette smoking by seventh-

TABLE 1.—Self-reported frequency (percent) of SLT use among two cohorts of 211 boys and 232 girls, Muscatine, Iowa, 1980–1984^a

Level of use by grade	Year of data collection									
	Boys					Girls				
	1980	1981	1982	1983	1984	1980	1981	1982	1983	1984
Never										
7th	84.4					99.1				
8th	78.8	71.6				99.1	98.2			
9th		64.6	64.2				96.4	92.8		
10th			51.5	56.6				93.0	95.5	
11th				43.3	53.7				92.6	90.9
12th					43.4					90.9
Occasional										
7th	14.6					0.9				
8th	21.2	25.6				0.9	1.8			
9th		30.2	34.0				3.6	7.2		
10th			44.3	41.5				7.0	4.5	
11th				46.7	39.8				7.4	8.2
12th					48.5					6.4
Weekly										
7th	0.0					0.0				
8th	0.0	2.8				0.0	0.0			
9th		2.1	0.9				0.0	0.0		
10th			3.1	0.9				0.0	0.0	
11th				0.0	4.6				0.0	0.0
12th					2.0					0.0
Daily										
7th	0.9					0.0				
8th	0.0	0.0				0.0	0.0			
9th		3.1	0.9				0.0	0.0		
10th			1.0	0.9				0.0	0.0	
11th				10.0	1.9				0.0	0.9
12th					6.1					2.7

^a Respondents were asked to indicate how often they used chewing tobacco or snuff on a six-point scale with response options ranging from "never" to "every day." Those who had tried SLT but used it less than once a week were classified as occasional users.

TABLE 2.—Prevalence (percent) of SLT use and cigarette smoking among seventh graders: Muscatine, Iowa, 1980 and 1985

Form and use	Boys		Girls	
	1980	1985	1980	1985
SLT ^a				
Never	82.4	40.6	98.5	82.1
Occasional	16.1	47.8	1.5	17.3
Frequent	1.5	11.6	0.0	0.5
Cigarettes ^b				
Never	71.8	46.2	75.5	52.6
Occasional (experimenter)	22.2	49.2	21.1	44.3
Weekly	7.1	4.5	3.4	3.1

^a In 1980, 205 boys and 197 girls were asked to indicate how often they used chewing tobacco or snuff. Those who used SLT less than once a week were classified as occasional users. When they reported weekly or daily use, they were classified as frequent users. In 1985, 207 boys and 196 girls were asked about lifetime SLT use. When they reported lifetime use of one to ten times, they were classified as occasional users. When they reported having used SLT more than ten times, they were classified as frequent users.

^b In 1980, 212 boys and 204 girls were classified according to use of cigarettes; in 1985, there were 199 and 192, respectively.

grade boys and girls from three Iowa communities. Because the stepwise procedure capitalizes on chance variation, we randomly selected and set aside 35% of the cases for cross-validation. We report the results from the analyses of the total sample as well as the classification results from the cross-validation analyses. For the classification analyses, prior probabilities were set to equal the proportion of cases in each group.

Predictors of Smokeless Tobacco Use

Because of the striking difference in prevalence of SLT use among boys and girls, we ran separate discriminant analyses to see whether different factors predispose their use of it. Respondents were divided into 2 groups according to their self-reported SLT use; respondents who reported never having tried SLT were classified as never users; those who had tried it even once were classified as SLT users. Table 3 reports the variables that best differentiated boys and girls who had never used from those who had tried SLT.

For boys, the discriminant function yielded a canonical correlation of .60 and a Wilks' lambda of .64. On this function, the centroid for the 152 never users was $-.83$, com-

TABLE 3. —Discriminant analysis results of boys' and girls' SLT use in 3 Iowa communities, 1984–1985

Sex	Step entered	Variable	Standardized discriminant function coefficient ^a
Boys	1	Cigarette smoking ^b	.71
	2	Alcohol drinking ^b	.44
	3	Mother smoking ^b	.27
	4	Female friend(s) smoking ^b	.25
	5	Attachment to mother ^c	.25
	6	Smoking harmful to sports ability ^b	.20
	7	Educational aspiration ^c	-.17
	8	Head of household occupation ^c	.14
	9	Homework hours ^c	.11
	10	Brother(s) smoking ^b	-.11
	11	Social success index ^c	-.12
	12	Grade point average ^c	.12
Girls		Eigenvalue	.57
	1	Cigarette smoking ^b	.52
	2	Drug use legally wrong ^c	.31
	3	Alcohol drinking ^b	.24
	4	Mother smoking ^b	-.27
	5	Head of household occupation ^c	.24
	6	Sister(s) smoking ^b	-.28
	7	Parents' rules good ^c	.23
	8	Observance of laws a moral duty ^c	.27
	9	Attachment to hometown ^c	-.25
	10	Age ^b	-.27
	11	Female friend(s) smoking ^b	.24
	12	Social success index ^c	.27
	13	Attachment to friends ^c	.18
		Eigenvalue	.22

^a $P < .0001$.^b On these variables, higher scores reflect more of whatever was being measured (e.g., more smoking).^c On these variables, higher scores reflect less of whatever was being measured (e.g., less attachment).

pared with a centroid of .67 for 188 SLT users. Twelve variables were selected to differentiate these 2 groups. Boys who had tried SLT were more likely to have smoked cigarettes and drunk alcohol. They spent less time on homework and had lower grades but claimed greater educational aspirations and more social success in school. They also had a parent with a less prestigious occupation, were more likely to believe that smoking would hurt their sports ability, and were less attached to their mothers. Their mothers were more likely to smoke, but their brothers and best female friends were less likely to smoke.

For girls, the discriminant analysis produced a canonical correlation of .42 and a Wilks' lambda of .82. The 232 never users had a centroid of -.18, whereas the 135 SLT users had a centroid of 1.19 on the discriminant function. Thirteen variables were selected to differentiate girls who had never used from those who had tried SLT. Like boys, girls who had tried SLT had a parent with a less prestigious occupation and a higher probability of having tried cigarettes or alcohol. On the other hand, the girls whose mothers or sisters smoked cigarettes were less likely to try

SLT; those whose best female friends smoked were more likely to try it. The greatest difference from boys, though, was the girls' commitment to conventional values; those who agreed with parental or legal rules were less likely to try SLT. Those who were less attached to their friends but more attached to their hometowns were more likely to try SLT. Although the age range in the sample was small, girls who had tried SLT tended to be younger.

In the cross-validation, we correctly classified 79% of the original and 71% of the set-aside subsample of boys. For girls, we correctly classified 87% of the original and 83% of the set-aside subsamples. Closer inspection revealed errors primarily in classifying girls who had used SLT. In the original subsample, we were able to classify correctly 80% of the boys who used SLT but only 17% of the girls. In the set-aside sample, we classified correctly 73% of the boys but only 21% of the girls who had used SLT.

Predictors of Cigarette Smoking

To parallel the analyses for SLT, we ran separate stepwise discriminant analyses on smoking for seventh-grade boys and girls. In these analyses, we sought to differentiate boys and girls who were never smokers, experimenters, and weekly smokers. Responses to three questions were used for determining membership in these groups. Those who reported never having smoked on the frequency and quantity question and who described themselves as nonsmokers were classified as never smokers. Those who reported smoking at least once a week were defined as regular smokers. Those who smoked less often than once a week were classified as experimenters. Nine respondents who provided inconsistent responses were excluded from subsequent analyses. Results are reported in tables 4 and 5.

For boys, two discriminant functions were significant (table 4), as were the differences among the three centroids. The first discriminant function provided the greatest discrimination between the 15 weekly and 172 never smokers. Boys who were weekly smokers were distinguished from the never smokers by having tried alcohol or SLT, having male or female friends or a brother who smoked, and having less success in or commitment to school (as reflected by

TABLE 4. —Summary statistics from discriminant analyses of seventh-grade boys' and girls' smoking groups, 1984–1985

Summary statistics	Boys		Girls	
	Function 1	Function 2	Function 1	Function 2
Centroids				
Never smoker	-.84	-.23	-.86	.19
Experimenter	.62	.39	.73	-.38
Weekly smoker	3.31	1.40	3.61	1.24
Eigenvalue	1.02	.18	1.22	.15
Percent of variance in discriminant space	84.68	15.32	89.09	10.91
Canonical R	.71	.39	.74	.36
Wilks' lambda	.42	.84	.39	.87
Chi-square	289.01	56.05	239.97	35.67
Degrees of freedom	20	9	34	16
P	.0001	.0001	.0001	.003

TABLE 5.—Predictors of seventh-grade boys' and girls' cigarette smoking status, 1984–1985

Sex	Step entered	Variable	Standardized discriminant coefficient	
			Function 1	Function 2
Boys	1	Alcohol drinking ^a	.38	-.15
	2	SLT ^a	.44	.76
	3	Female friend(s) smoking ^a	.25	-.22
	4	Smoking harmful to sports ability ^a	-.15	.37
	5	Smoking dangerous to health ^b	.28	-.29
	6	Brother(s) smoking ^a	.14	.37
	7	Grade point average ^b	.19	-.08
	8	Homework hours ^b	.17	-.09
	9	Male friend(s) smoking ^a	.22	-.05
	10	Observance of laws a moral duty ^b	.09	-.19
Girls	1	Female friend(s) smoking ^a	.30	.11
	2	Alcohol drinking ^a	.42	.07
	3	Grade point average ^b	.31	.00
	4	Brother(s) smoking ^a	.33	.01
	5	Attachment to hometown ^b	.26	.22
	6	SLT ^a	.14	-.57
	7	Age ^a	.27	-.02
	8	School trouble index ^b	-.10	-.47
	9	Religiousness ^b	.02	.39
	10	Concern for teachers' appraisal ^b	-.13	.44
	11	Parents' rules good ^b	.09	-.35
	12	Male friend(s) smoking ^a	.16	-.19
	13	Attachment to father ^b	.18	-.05
	14	Mother smoking ^a	.17	.05
	15	Smoking harmful to sports ability ^a	.05	.27
	16	Social success index ^b	.11	.25
	17	Attachment to friends ^b	-.16	.01

^a On these variables, higher scores reflect more of whatever was being measured (e.g., more drinking).

^b On these variables, higher scores reflect less of whatever was being measured (e.g., student was less likely to believe smoking hurts sports ability).

grades and amount of time devoted to homework). Weekly smokers were less likely than never smokers to believe that smoking endangered their health or hurt their sports ability. They were also less likely to believe that one had a moral duty to obey the law.

The second discriminant function differentiated most between boys who were weekly smokers and the 153 who were experimenters. The variables that increased the probability that a boy was an experimenter, rather than weekly smoker, were: having used SLT, having a brother who smokes, and believing that smoking hurts sports ability or endangers one's health. On the other hand, boys were more likely to be weekly smokers than experimenters if they had female friends who smoked.

For girls, two discriminant functions were significant, and again, the differences among the three centroids were significant. The first discriminant function provided the greatest discrimination between the 144 who never smoked and the 12 who smoked weekly. Girls were more likely to be weekly than never smokers if substance use was relatively common in their environment: using SLT or alcohol themselves, or having female or male friends, mothers, or brothers who smoke. Being older and feeling a close attachment to their friends also increased the likelihood of being a weekly smoker, but having good grades and feeling more attached to their fathers or hometowns decreased that likelihood for girls.

The second discriminant function accounted for little variance in the discriminant space (table 4). It distinguished most between girls who were weekly smokers and those 111 who were experimenting. Weekly smokers were less likely than experimenters to have tried SLT or to be religious. They cared little about what teachers thought and had more trouble and less social success in school. They were also more likely to believe that smoking hurts sports ability and that their parents' rules are good enough.

In the cross-validation analyses, the discriminant functions correctly classified 76% of the boys and 77% of the girls overall in the original subsample. In the set-aside subsample, we were able to classify 67% of the boys and 64% of the girls overall. In both the original and set-aside samples, a large number of girls who were experimenters were misclassified as never smokers (31% in the original and 53% in the set-aside sample). In the latter sample, 87.5% of girls who were weekly smokers were misclassified as experimenters.

CONCLUSIONS

Our data, consistent with other recent reports on the prevalence of SLT use among adolescents, suggest that boys are more likely than girls to use SLT and more likely to use it as they get older. Use by male adolescents has increased over the last several years.

Many of the predictors of boys' smoking were the same as those for girls', and none of the predictors of smoking had opposite effects for boys and girls. This is in contrast to the results from the discriminant analyses for boys' and girls' use of SLT; few of the predictors for boys' were the same as those for girls' use. The exceptions were trying alcohol or smoking, having a parent with a less prestigious occupation, or having more social success in school; for boys and girls these increased their likelihood of using SLT. If their same-sex sibling smoked, boys and girls were both less likely to try SLT. Two predictors had opposite effects on boys' and girls' SLT use: if their mothers smoked, boys were more and girls less likely to have tried SLT; if their best female friend smoked, girls were more and boys less likely to try it. Less academic commitment and achievement increased the probability that boys would use SLT but were unrelated to girls' use. Questioning conventional values increased the likelihood that girls would try SLT but was unrelated to boys' use. We did much better in predicting boys' use than that of the girls. We only explained 18% of the variance in girls' use, compared with 36% of the variance for boys.

When we compared the predictors of boys' smoking and SLT use, we found that boys who had tried one form of tobacco or alcohol were more likely to have tried the other form of tobacco. Boys who were weekly smokers or SLT users spent less time on homework and had lower grades. On the other hand, several variables had opposite effects on boys' smoking and SLT use. Those who smoked were more likely to have a female friend or brother who smoked, than were those who used SLT. Those who smoked were less likely to believe that smoking hurt sports ability; those who used SLT were more likely to believe this. Educational aspirations and popularity with classmates were related to SLT use but unrelated to smoking.

There were few similarities in the predictors of smoking and SLT use among girls. Besides trying alcohol and the other form of tobacco, only the association with a female friend who smoked was related to both the smoking and SLT. A large number of variables were related in opposite ways to their smoking and SLT use. Girls who smoked were more likely to have a mother who smoked than those who had tried SLT. Girls who smoked were older; girls who had tried SLT were younger. Girls who smoked had less social success in school; girls who used SLT were more popular with classmates. Girls who smoked were more attached to friends and less attached to their hometown; girls who used SLT were less attached to friends and more attached to their hometown. Smoking by male friends and brothers was related to girls' smoking but not to their SLT use. Lack of commitment to conventional values was more highly related to girls' use of SLT.

Given these results, we would expect the typical adolescent SLT user to be a male who has experimented with alcohol and cigarettes. His mother is more likely to smoke, but his brother and best female friend are less likely to smoke. He has less academic success, although he has higher educational aspirations and perceives himself to be more popular with classmates. He is also more likely to believe that smoking hurts sports ability. The typical adolescent smoker is not necessarily male. Nevertheless, if we focus only on boys for purposes of comparison, we see that

the typical adolescent male smoker is similar to the typical SLT user because he too is likely to have experimented with alcohol and cigarettes. He, like the SLT user, is less likely to spend time on homework and more likely to earn low grades. Boys who are weekly smokers are more likely than SLT users to have friends and brothers who smoke. They are also less likely to believe that smoking hurts sports ability.

These findings have a number of implications for the prevention of SLT use. First, taken together, the small amount of variance we accounted for in girls' SLT use and the dissimilarities between predictors of their smoking and SLT use indicate that interventions for preventing smoking may not reduce girls' SLT use. Clearly, we need more research on psychosocial correlates of girls' SLT use if we are to design effective programs for preventing it. However, those conducting prevention programs may want to consider the tendency of female SLT users to question parental and legal rules. This finding suggests that girls' SLT use is perceived as more rebellious than is that of boys. Put another way, unlike boys' tobacco use, girls' SLT use, and to a lesser extent their smoking, may be a form of rebellion against societal strictures. On the other hand, the greater similarity among predictors of boys' SLT use and their smoking suggests that similar interventions are effective for both. However, we should note that prevention programs that try to convince boys that smoking will hurt their sports ability may reduce their smoking but increase their use of SLT as a substitute, unless they are convinced that SLT use will hurt their athletic performance as well.

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Marketing Smokeless Tobacco in California Communities: Implications for Health Education^{1, 2}

Marc T. Braverman,³ Carol N. D'Onofrio,⁴ and Joel M. Moskowitz^{4, 5}

ABSTRACT—In the first phase of a 5-year research project aimed at curtailing smokeless tobacco use among youth, we examined the marketing of smokeless tobacco within California. Observational data were collected from almost 200 retail stores located near high schools and colleges in 14 California counties. Interviews were conducted with over 100 school personnel and youth leaders in 13 counties and with seven retailers from 4 counties. Overall, 81% of the stores in the sample carried smokeless tobacco, and even in urban areas most stores (71%) had these products for sale. Urban stores were more likely to have materials promoting them (e.g., posters, displays, coupon offers). Almost all (98%) stores that carried smokeless tobacco sold moist snuff. Most (78%) school personnel and youth leaders, especially in urban areas, were aware of advertisements for it, particularly on television and in magazines. Rogers' theory regarding the diffusion of innovations was the basis of the discussion of our results. The implications of marketing for the development of health education programs are examined.—NCI Monogr 8:79-85, 1989.

The tobacco industry attributes much of the credit for recent jumps in SLT consumption to "well planned and executed marketing and advertising strategies" (1). Concerned health professionals also recognize its visibility and advertising as major factors in increased prevalence and use (2-5). Therefore, the promotion of such tobacco products is a force that must be considered in the design of prevention programs. In this report, we provide an initial exploration of marketing issues, investigating the availability and salience of SLT across communities, as well as the perceptions of community informants regarding product advertising and promotion. These findings are discussed with regard to the

development of community-based interventions to curtail SLT use among youth.

An understanding of product availability and production is particularly important for an educational program intended for delivery throughout a state as geographically, demographically, and socially diverse as California. A critical question is whether the marketing of SLT varies by region within the state, for this might well affect exposure to products, inducements to use them, and, ultimately, use patterns.

These issues were investigated within a larger program of exploratory research undertaken by the staff of Project 4-Health as the first phase of a 5-year project aimed at curtailing the use of SLT among California youth. Data were gathered to address the following questions:

- 1) How widely available are various forms of SLT in California communities? Operationally, availability was assessed in the percentage of retail stores carrying snuff and chewing tobacco, the types and brands stocked, and the pricing of these products. The latter variable was included because adolescents, having limited funds, are likely to respond to variations in product prices, as has been found in the case of cigarettes (6).
- 2) Is the availability of SLT related to differences in community size and "urbanicity"?
- 3) Are there regional differences in the promotion of SLT? Here both point-of-sale inducements and community perceptions of advertising and other promotional activities were considered.

Variability in these dimensions of marketing would have clear implications for targeting prevention efforts to youth within California, as well as for matching program content to the degree of young people's exposure to SLT and its commercial promotion.

METHODS

Project 4-Health is a multiphase research and intervention study being collaboratively conducted by the School of Public Health at the University of California, Berkeley, and the California 4-H program, a unit of University of California Cooperative Extension. In each of California's 58 counties, the 4-H program is administered by university academic personnel known as 4-H advisors, who are knowledgeable about their communities and generally familiar with techniques of objective data collection. Advisors from 13 counties were invited to participate in the exploratory research that initiated Project 4-Health. These counties were purposefully selected to represent a range

ABBREVIATIONS: SLT = smokeless tobacco; *R* = coefficient of multiple correlation.

¹Supported by Public Health Service grant CA-41733 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

²Address reprint requests to: Project 4-Health, University of California, 1919 Addison St., Suite 204, Berkeley, California 94704.

³Department of Applied Behavioral Sciences, University of California, Davis, California 95616.

⁴School of Public Health, University of California, Berkeley, California 94720.

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of urbanicity, size, demographic population characteristics, and geographic location.

After receiving training on the specific methods and instruments to be used, participating advisors assisted by graduate students interviewed key informants in their counties about SLT and completed structured observations concerning its availability in local communities. Project staff completed additional observations in a 14th county; the data were collected during June and July 1986.

Formal Observations

Sample selection.—Within each county, the advisor selected two municipalities; the largest city (or town) and a small-to-moderate-sized town. In each municipality, one public high school was randomly selected. Exceptions were made for large cities, and thus four high schools were selected in Los Angeles, whereas two were selected in both San Francisco and San Jose. Local college campuses also were chosen as observation areas in smaller communities.

Around each selected school, an "observation area" extending three to five blocks in each direction was mapped out and used to define the sampling frame for retail establishments. Within this area all supermarkets, convenience, drug, and liquor stores were listed, and two stores from each category were randomly selected for observation. Most areas had fewer than two stores in one or more of the categories, and, in the final sample, the number of total stores selected per area ranged from one in residential areas to eight in commercial areas. In those communities in which only one or two stores were in the surrounding area of the selected high school, the advisor selected for observation a third community within the county as well. Altogether, observations were completed in 199 retail stores around high schools and college campuses in 43 observation areas located in 14 California counties.

Instrumentation and procedure.—The instrument for formal observations of retail establishments was a checklist that included, in addition to the location and type of store, the following variables:

- 1) The number of varieties of the following kinds of products: moist snuff, moist snuff pouches, "loose-leaf chew," plug, and dry snuff. For each product, one of the following categories was checked: No varieties present, one or two varieties present, three or more varieties present.
- 2) The presence of posters, displays, or other inducements to buy SLT.
- 3) The location of SLT products within the store.
- 4) The products adjacent ("within two feet") to the SLT products.
- 5) The presence of "look-alike" products, e.g., bubble gum or beef jerky processed and packaged to resemble moist snuff or loose-leaf chew.
- 6) The price of selected brands of various types of SLT.

If the store owner or manager refused to allow information to be recorded, the advisor selected an alternate store. Data collection was interrupted in fewer than 2% of the stores visited.

Data analysis.—In analyzing data from the formal observations of SLT in stores, we used the local community (operationally defined here as the observation area) as the conceptual unit. Therefore, for most of the variables, scores were averaged across all stores within each observation area to produce community means ($n = 43$). Preliminary data analysis revealed that the category "drug store" included two distinct clusters: large chain drug stores, which sell a wide variety of nondrug products, and local pharmacies. Thus this category was subdivided for analysis.

Using multiple regression, we analyzed the data to determine whether product availability and price could be predicted from selected community descriptors. The following were designated as dependent variables: (1–5) the means for each community on the availability index for, respectively, moist snuff, snuff pouches, loose-leaf chew, plug, and dry snuff; (6) the percentage of stores in a community that carried any SLT products; (7–10) the average price for a representative brand of moist snuff, snuff pouches, loose-leaf chew, and plug; and (11) the number of store-based inducements to purchase SLT. (The numbers in parentheses refer to the numbers given to the variables.)

The independent variables were categorized into two blocks. Block 1 described the stores within the observation area that contributed the data. Four variables were created reflecting the percentage of the kinds of stores within the observation areas sampled (i.e., percentage of supermarkets, convenience stores, etc.). A fifth variable was the total number of stores sampled in the observation area.

Block 2 included three variables that pertained to the community itself. Population size was included by the ranking of numbered municipalities associated with each observation area, with "1" being assigned to Los Angeles. Observation areas within the same city were coded with the same rank. The population size of municipalities represented in the sample ranged from 2,900 to over 3 million.

To represent an urbanicity dimension, we rank-ordered counties in the percentage of the county's population that lives in Census-defined "urban areas," with "1" being the highest and "14" the lowest. We created a third variable, representing the interaction between community size and urbanicity for each community by calculating the product of its urbanicity and size rankings. Thus high values represented small towns in rural counties, whereas low values represented large cities in urban counties. The level of educational institution that formed the core of the observation area, high school or college, was not an even marginally significant predictor for any of the dependent variables and was omitted from the analyses reported here.

A hierarchical procedure was used in which block 1 variables were entered first, followed by block 2. For statistical reasons, we deemed it more meaningful to present the change in R^2 for the block as a whole rather than break it down into the contribution from each component variable.

Interviews

Within the selected counties, advisors drew upon their knowledge of the community, resource lists, and recommendations from others to arrange interviews with key informants in several categories: school personnel, youth

leaders, health professionals, youth, and young adult users of SLT. As time and access permitted, interviews also were conducted with retail personnel in stores selling the products. Six types of interview forms were prepared that corresponded to the six categories of informants and included both open-ended and fixed response items. All those interviewed provided informed consent. If the informant agreed, interviews were tape-recorded. The interviews averaged approximately 30 minutes in length.

Responses to selected items from interviews with school personnel and youth leaders were copied verbatim from interview forms and audiotapes and were subjected to content analysis for identification of variables and related coding categories. All responses were then coded according to a common system. Descriptive and nonparametric statistics were used for analysis of the results.

RESULTS

The report of results is organized to highlight the following components of marketing: product placement, product diversification, price, point-of-sale inducements, and advertising and promotion. The tables summarize findings from the observations. Table 1 presents descriptive results at the store level for the 199 stores; table 2 shows the correlations among observed variables, when the 43 communities (i.e., observation areas) were used as the units of analysis; and table 3 gives the results of the hierarchical regression analyses, also with the community as the unit of analysis.

Placement

One component of product placement is the type of store in which it is sold. As table 1 shows, in areas around schools,

over 90% of the supermarkets and liquor stores, as well as over 80% of convenience and chain drug stores, carry some form of SLT product; however, almost no pharmacies did so.

Another aspect of placement concerns the location of these products within the 161 stores that carry them. The SLT was adjacent to 1) cigarettes in 62%, 2) candy or snacks in 42%, and 3) alcohol in 23%. (This latter figure is heavily weighted by observations in liquor stores.) These proportions exceed 100%; typically, several product types are adjacent in each case. In many stores, SLT was kept behind the counter or near the cash register to prevent shoplifting, which was repeatedly cited by retailers as a significant problem. In some stores, moist snuff was kept in refrigerated cases to prevent dehydration. This was found most often in stores in large towns and near college campuses that were associated with a more sophisticated clientele, according to several retailers.

The characteristics of the communities in which SLT is found were explored in the regression analyses (table 3). Within a community, the percentage of stores that carry some form of it was related to both the type of stores in the community (block 1, $R^2 = .276$, $P < .05$) and the urbanicity and size of the community itself (block 2, $R^2 = .174$, $P < .05$). The coefficients of the three variables in block 2 were all significant, which indicated a complex relationship between town size, urbanicity, and the size-urbanicity interaction. Follow-up analysis of the interaction revealed that large cities in urban counties had the lowest percentage of stores selling SLT (an average of 71% across the communities that fit this classification), whereas large cities in rural counties (91%) and small towns in urban counties (87%)

TABLE 1.—Descriptive observation information, store-level data

Variable	Supermarket	Convenience store	Pharmacy	Chain drug store	Liquor store	Total
No. in sample	60	51	19	28	41	199
Percent of stores in which any SLT is sold	92	84	5	88	95	81
Percent of stores carrying						
Moist snuff	90	82	5	88	82	79
Snuff pouches	78	67	5	88	82	71
Loose leaf chew	83	57	5	85	86	70
Plug	68	31	0	51	82	51
Dry snuff	37	0	0	10	61	22
Percent of stores carrying SLT displaying inducements to purchase	25	30	100 ^a	26	46	32
Percent of stores with a look-alike product	15	24	0	14	20	17
Percent of stores carrying SLT in which it is adjacent to						
Cigarettes	65	67	100 ^a	74	44	62
Alcohol products	11	12	0 ^a	13	59	23
Candy or snacks	35	51	100 ^a	35	44	42
Mean price \pm SD						
Can moist snuff	1.24 \pm .14	1.35 \pm .11	1.36 ^a	1.32 \pm .11	1.32 \pm .09	1.30 \pm .12
Can snuff pouches	1.21 \pm .12	1.36 \pm .10	1.36 ^a	1.30 \pm .14	1.31 \pm .10	1.29 \pm .13
Package of chew	1.04 \pm .10	1.22 \pm .15	—	1.10 \pm .08	1.16 \pm .12	1.12 \pm .13
Package of plug	.99 \pm .12	1.14 \pm .17	—	1.09 \pm .12	1.08 \pm .19	1.06 \pm .16

^a Only one case was in the subcategory of pharmacies carrying SLT.

TABLE 2.—Zero-order correlation matrix for community-level observational variables

Variable	2	3	4	5	6	7	8	9	10	11	12	13
1. No. of varieties moist snuff	.72 ^a	.64 ^a	.30 ^b	.13	-.87 ^a	.42 ^a	.19	.24 ^c	.26 ^b	.44 ^a	.25 ^c	.42 ^b
2. No. of varieties snuff pouches	1.00	.64 ^a	.50 ^a	.08	-.68 ^a	.52 ^a	-.03	.01	.37 ^a	.48 ^a	.33 ^b	.21
3. No. of varieties loose-leaf chew		1.00	.62 ^a	.35 ^a	-.66 ^a	.37 ^a	.11	.03	.18	.25 ^c	.16	.09
4. No. of varieties plug			1.00	.36 ^a	-.42 ^a	.10	.13	.03	.08	.07	-.12	.22
5. No. of varieties dry snuff				1.00	-.08	-.20	.00	-.05	-.27 ^b	-.23 ^c	-.19	-.30 ^b
6. Percent of stores with no SLT					1.00	-.35 ^b	-.27 ^b	-.31 ^b	-.40 ^a	-.40 ^a	-.31 ^b	-.20
7. No. of store-based inducements						1.00	-.21 ^c	-.13	.44 ^a	-.51 ^a	.17	.31 ^b
8. Community urbanicity							1.00	.60 ^a	-.07	-.12	-.11	.00
9. Community size								1.00	.09	.01	.09	.11
10. Average price, can of moist snuff									1.00	.86 ^a	.57 ^a	.76 ^a
11. Average price, can of snuff pouches										1.00	.39 ^a	.58 ^a
12. Average price, package of loose-leaf chew											1.00	.66 ^a
13. Average price, package of plug												1.00

^a $P < .01$.^b $P < .05$.^c $P < .10$.

had the highest percentages. Both slightly exceeded small towns in rural counties (85%). Thus, although as a group these factors significantly predict availability, availability does not increase linearly as community size or urbanicity decrease.

Product Diversification

In view of the marketing emphasis on moist snuff, we examined the number of brands available for each type of SLT product, hypothesizing that the variety of moist snuff brands would be greater than the variety of other SLT types. This expectation was confirmed by the community averages on the 3-point index of availability completed for each store (0 = no brands present; 1 = one or two brands; 2 = three or more brands). Across all communities, moist snuff stood highest (1.42), followed by loose-leaf chew (1.15), snuff pouches (.84), plug (.63), and dry snuff (.27).

Because 63% of the observed stores were coded as stocking "3 or more" brands of moist snuff, it is likely that a moderate ceiling effect existed in the data. In some stores, the actual number of brands ranged as high as six or seven. For the other product types such as chew and plug, a large variety of brands was much less common. If a wider range had been incorporated at the upper level of the scale, moist snuff would probably show even greater product diversification than is indicated here, but other smokeless products would probably not show substantial change. The number of varieties of moist snuff, snuff pouches, and loose-leaf chew were all strongly intercorrelated (table 2). A wide variety of one form in a given community was associated with a wide variety of the others.

As shown in table 3, regressions were conducted for each type of SLT so we could determine whether the presence of different varieties could be predicted from either store

TABLE 3.—Increments in R^2 for hierarchical regression equations^a

Dependent measure	R^2 , block 1	P , block 1	R^2 , block 1 + block 2	R^2 change	P , block 2
Average availability index					
Moist snuff	.155	NS ^b	.365	.209	<.02
Snuff pouches	.314	<.02	.385	.071	NS
Loose-leaf chew	.281	<.05	.383	.102	NS
Plug	.467	<.001	.486	.019	NS
Dry snuff	.343	<.01	.378	.035	NS
Percent of stores with no SLT	.276	<.05	.450	.174	<.05
Store-based inducements	.319	<.02	.359	.040	NS

^a Note: Independent variables constituting block 1 (all except 5 expressed as percentage) include: 1) supermarkets; 2) convenience stores; 3) pharmacies; 4) chain drug stores; 5) No. of stores in observation area.

Independent variables constituting block 2 include: 1) size of city or town (by rank); 2) urbanicity of county (by rank); 3) interaction of size-urbanicity.

^b NS = not significant.

type or community characteristics. For all products *except* moist snuff, store type accounted for a significant proportion of variance, whereas community characteristics did not. For moist snuff, community characteristics predicted variety, but store type did not. Furthermore, the main effects for town size, county urbanicity, and the size-urbanicity interaction all produced significant coefficients.

In 17% of all stores, a look-alike product, usually bubble gum packaged to resemble chewing tobacco, was sold. The other major type of look-alike product was beef jerky cut like moist snuff and sold in small round tins. Nearly one of every four convenience stores stocked some form of look-alike product.

Price

Table 1 shows the average prices and standard deviations for each form of SLT product, categorized by type of store. Prices for chewing tobacco appear more likely to vary across sites than prices of snuff. Store type accounted for a significant amount of variance ($P < .01$) for snuff pouches and for a marginally significant ($P < .10$) proportion of variance for moist snuff with prices being lower in supermarkets than in other stores. Store type did not account for a significant amount of variance for loose-leaf chew or plug tobacco. More important, community characteristics did not account for a significant amount of variance for any of the products. This indicates that product prices do not vary appreciably across the dimensions of town size or urbanicity.

Point-of-sale Inducements

In general, some form of inducement (posters, special displays, or tear-off coupon offers) was present in 32% of the stores that sold SLT (table 1). Furthermore, as table 2 shows, inducements were more likely to be present in urban than in rural stores ($r = -.21$), and they were moderately correlated with higher prices for moist snuff, moist snuff pouches, and plug tobacco. The results of the regression analysis for point-of-purchase inducements are given in table 3. Store type accounted for a significant proportion of variance. Inducements were most prevalent in liquor stores, followed by convenience stores.

Advertising and Other Promotion in the Community

Over 78% of the school personnel and youth leaders interviewed had seen advertisements for SLT. The proportion of respondents having seen advertisements was greater in urban than in rural counties. Fifty-seven percent of the respondents named specific brands that they had seen or heard advertised. The proportion of youth leaders naming brands was significantly greater in urban counties (76.9%) than in rural ones [38.5%; $\chi^2(1) = 7.88$; $P < .01$], but no urban-rural differences were found among school personnel on this variable. Seven specific brands were identified, with Skoal (including Bandits) accounting for 44.6% of all that were mentioned and Copenhagen accounting for another 26.5%.

Slightly over 50% of the interviewees who had seen SLT advertisements reported seeing them in magazines. A significantly greater proportion of respondents from urban

(60%) than from rural counties (38%) mentioned this source [$\chi^2(1) = 3.89$; $P < .05$]. Particular magazines mentioned were most often related to sports, agriculture, and automobiles. Also mentioned were magazines on camping, outdoor life, and fishing, as well as men's magazines, trade journals, and general magazines. Only 6 respondents said they had seen SLT advertised in newspapers, and this was typically in the Sunday magazine section.

Nearly 1 of every 4 respondents mentioned seeing SLT advertised in stores, particularly commenting on eye-level displays at cash registers and signs at check-out stands in liquor and convenience stores. In addition, about 20% of those interviewed claimed they had seen it advertised on billboards. Interviewees from 10 counties described advertisements for it at special events such as rodeos, car races, car shows, sporting competitions, and county fairs. Promotional devices in these instances included signs, banners, posters, bandannas, and decals on beer glasses offered for sale, as well as overall sponsorship of the event. Respondents who mentioned seeing SLT advertised on television frequently described similar promotional methods on television broadcasts of sporting events.

Awareness of the distribution of free samples was reported by 30% of the respondents. The proportion observing free sample distribution was greater in urban than in rural counties. Two-thirds of those who knew of this promotional technique named specific brands. Seven brands were identified, with Skoal Bandits (40%), Skoal (24%), and Copenhagen (12%) being the most widely reported. Public events were most frequently named as places where free samples were given away. These included county fairs, baseball games, regional events, auto shows, and farm equipment and livestock shows.

An important issue related to marketing is the sale or free distribution of tobacco to minors, which is forbidden by California State law. A number of respondents expressed concern about this topic, with regard to SLT. For example, one reported that a distributor at an air show in a rural county was "passing it out to anyone." Another respondent said that her son came home with free samples given away in oil fields.

DISCUSSION

Clearly, SLT has penetrated markets throughout California, and it is present to a very high degree in the community environments of youth. Some form was offered for sale by 81% of the stores near high schools and college campuses in 43 geographically diverse areas. If pharmacies are excluded, this percentage rises to 90. Illustrating the striking degree to which moist snuff leads the SLT market, all but 4 of the 161 stores in our sample that had some form for sale also carried moist snuff. In addition, the advertising and promotion of it appear nearly as pervasive as the product.

The finding that the proportion of stores carrying SLT was lower in large cities within urban counties (71%) than in other types of communities may reflect urban-rural differences in use rates found in national and regional surveys (7). Still these data show that it is readily available even in urban areas and suggest that efforts are under way to increase demand in metropolitan communities. Point-of-sale

inducements were more prevalent in urban areas, and urban respondents were 1) more aware of SLT advertising than were those in rural areas, 2) more likely to identify advertisements from multiple sources, and 3) knew of more free sample distributions.

Variations in the convenience store category may explain why SLT was found in a slightly higher proportion of stores in large cities within rural counties (91%) and small towns within urban counties (87%) than in small towns in rural counties (85%). In larger towns and urbanized counties, convenience stores almost invariably belong to large chains which, like the tobacco industry, use modern marketing techniques, including incentives for their sales force (8). However, convenience stores in rural towns also include a percentage of small, independent, general stores with less systematic product stocks and less aggressive marketing approaches.

A critical issue is whether marketing practices influence youth to use SLT. The results of this study, interpreted in light of research on the diffusion of innovations (9), may be useful in describing the growing popularity of these products, particularly moist snuff, among youth.

The ready availability of moist snuff would appear to be a necessary, if not sufficient, condition for use by youth. Thus moist snuff is stocked by a high proportion of several types of stores near high schools and college campuses, whereas other forms are less widely available. Accessibility is additionally assured by distributors locating moist snuff in convenience stores, chain drug stores, and supermarkets that youth visit frequently. Users thus are able to obtain the product with little effort, and nonusers are continually exposed to SLT. According to Rogers (9), such awareness or knowledge is the first stage in the process of adopting an innovation.

The finding that SLT was frequently found next to cigarettes, candy, snacks, or alcohol implies the association of moist snuff with other products purchased by consumers for pleasure. This association is likely to increase interest in the product, corresponding to the second or persuasion stage of the adoption process. Awareness and interest are enhanced by advertising, which portrays the association of SLT with attractive role models, and by product sponsorship of exciting events. Creative packaging and point-of-purchase inducements arouse additional interest in a setting where the opportunity to try moist snuff is readily available. Decision and implementation, the third and fourth stages of the adoption process, may well be influenced by these factors.

Trial of SLT is facilitated in numerous ways. Product diversification enables the experimental user to exert his individuality by exercising choice. Moreover, if an initial trial is not satisfactory, the experimenter can try another form. Moist snuff pouches initiate the new user to SLT in pre-measured amounts and minimize problems of controlling loose tobacco in the mouth. Instructions distributed at the point of purchase with free samples and television advertising guide the experimenter through early use experiences. The provision of free samples and modest product pricing permit trial to occur at little or no cost. Very young or tentative experimenters may begin by using familiar products processed and packaged to look like SLT.

Advertising again is important in establishing confirmation, the final stage of adoption. In addition to the identification of self with attractive role models seen in advertisements, the new user finds himself identified with other users in the community and with a culture promoted by banners, hats, and T-shirts sporting brand names and slogans.

The evaluation of moist snuff after experimental use thus involves much more than simple like or dislike of the product. Newfound status, self-identification, and social acceptance all contribute to the user's decision to use the product again. Because these benefits meet major developmental needs of adolescents, youth who experiment with moist snuff may be especially prone to continue use. With the gradual development of addiction, physiologic processes augment social-psychological reasons for use and take over as primary factors in habit maintenance. Finally, increases in the number of local adopters are likely to stimulate adoption by others.

In summary, designers of programs to prevent and reduce the use of SLT among youth must recognize the high availability and visibility of moist snuff within young people's immediate environments. The results of this study indicate that moist snuff is no longer a new or unfamiliar product in California communities. It is widely available in urban and rural areas, and in a variety of flavors, forms, and packages. More traditional forms of SLT are also available throughout the State, but in fewer stores.

The promotion of SLT, and particularly moist snuff, is also pervasive. A range of marketing practices promotes adoption of the SLT habit; therefore, programs aimed at prevention must be sensitive to the local context in which information about it appears and must be flexible enough to permit consideration of local customs and culture related to its use. Prevention programs must recognize, as the tobacco industry has (4), that America is not so much a mass market as a collection of micromarkets. An analysis of the strategies through which SLT is promoted in local communities can help us identify high-risk target groups, as well as various potential intervention points.

Additional research is needed on the relationship between product availability and use. Further research is also needed on other dimensions of the community context for SLT use, requiring conceptualization that expands upon models of peer pressure and social modeling. The results of this study support what we consider to be an important new direction for research and intervention relating to the SLT problem.

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Advertising and Promotion of Smokeless Tobacco Products¹

Virginia L. Ernster^{2, 3}

ABSTRACT—This paper is focused on the approaches used to advertise and promote smokeless tobacco products during the early to mid-1980s. These included traditional motifs that featured rugged-looking masculine models in sporting and outdoor settings as well as an expanded white-collar appeal. Smokeless tobacco was not affected by the ban on broadcast advertising of cigarettes that went into effect in 1971, and, until 1986, both print and broadcast media were used to advertise it. Promotional activities ranged from sponsorship of sporting events to offers for clothing bearing smokeless tobacco product logos. Despite the claims of manufacturers that advertising and promotional efforts were not targeted to youth, smokeless tobacco companies sponsored tobacco-spitting contests with teenage participants, a college marketing program, and college scholarships. In efforts that appeared designed to bolster their public image in the face of growing concern over the consequences of smokeless tobacco use by young people, companies like U.S. Tobacco Company contributed to major social programs, including, ironically, alcohol- and drug-abuse prevention programs. Spurred by public health groups, federal legislation was passed in 1986 that banned television and radio advertising of smokeless tobacco products and required manufacturers to include warning labels on their products on the potential health hazards of smokeless tobacco use.—NCI Monogr 8:87-94, 1989.

Given the increased prevalence of SLT use among young males in recent years, growing concern has been expressed about the role of advertising and promotion in fostering such use (1-5). Between 1970 and 1985, the domestic production of all forms of SLT increased 42%, and the production of fine-cut tobacco, used in moist snuff, tripled (6). From 1980 on, the increase in sales was largely a function of a continuing increase in the moist snuff category; loose-leaf sales increased slightly until 1984 and then declined. All other categories (plug, moist plug, dry snuff, twist/roll, and loose leaf) declined over the same period (7, 8), as shown in table 1. Although firm data on SLT advertising and promotional expenditures are not readily available, various estimates have been published. In 1984, an estimated \$8 to \$10 million was spent on advertising by U.S. Tobacco alone (9, 10), with estimates of industry-wide

advertising expenditures for that year ranging from \$20 to \$31 million (11, 12). It appears that moist snuff experienced the greatest proportional increases in advertising of all the major categories of SLT.

The U.S. Tobacco Company, which commands nearly 90% of the domestic moist snuff market (8), introduced a variety of new SLT products, most notably those in the Skoal Bandits line, and the company's advertising expenditures increased dramatically, from \$800,000 to \$4.6 million between 1972 and 1984 for television advertising alone (13). These efforts brought marked increases in sales of the company's moist snuff brands. By 1984, U.S. Tobacco had become a Fortune 500 company, ranking 485th in total sales but a high 44th in growth rate in earnings per share over the previous 10 years (14). By 1985, the company's ranking among the Fortune 500 had moved to 476th place (15).

In this paper, I describe the types and themes of SLT advertisements and promotions, address the issue of youth targeting in the advertisements and promotional activities, and review recent legislative efforts to limit its advertising in the United States. Focus is primarily on activities in the first half of the 1980s.

TYPES AND THEMES OF SMOKELESS TOBACCO ADVERTISING

Advertisements for SLT products have traditionally used a rugged, masculine image, reflective of the brand names of such products (e.g., Red Man, Kodiak, Chattanooga Chew, Applejack, Levi Garrett, Cannon Ball, and Country Blend). They have appeared in magazines that cater to the sporting and outdoor public, such as *Field and Stream*, *Road and Track*, and *Sports Illustrated*, and on sports programs on radio and television. As an official sponsor of the 1980 Winter Olympics, U.S. Tobacco spent \$2.5 million to promote snuff (16). For the 1984 Winter Olympics, the company sponsored a Sports Medicine Program and conducted a \$1-million ad campaign for Skoal Bandits that was aired during American Broadcasting Company's coverage of the games (16, 17).

For a time, professional athletes served as spokesmen for SLT products, including Pittsburgh Steelers quarterback Terry Bradshaw, Kansas City Royal George Brett, Texas Ranger Sparky Lyle, and Carlton Fisk of the Chicago White Sox (1, 18). New York Yankee Bobbie Murcer recorded the song "I'm a Skoal-dipping Bandit" (19), and popular country musician Charlie Daniels has appeared in advertisements for U.S. Tobacco's smokeless products (20).

Industry representatives have publicly described product design and promotional strategies developed to attract new types of consumers. The president of Helme Tobacco Com-

ABBREVIATION: SLT = smokeless tobacco.

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²Department of Epidemiology and International Health, 1699 HSW, School of Medicine, University of California, San Francisco, California 94143-0560.

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TABLE 1.—SLT sales in thousands of pounds, 1981–1985^a

Category	1981	1982	1983	1984	1985
Plug	11,348.0	10,249.0	9,578.0	8,687.0	8,019.0
Moist plug	6,519.0	5,073.0	4,357.0	3,956.0	3,842.0
Dry snuff ^b	11.8	11.2	10.7	10.2	9.5
Moist snuff and fine cut ^b	30.2	32.7	35.0	37.5	39.1
Twist/roll	1,861.0	1,767.0	1,709.0	1,632.0	1,516.0
Loose leaf	70,519.0	70,886.0	70,924.0	72,976.0	71,732.0
Total	132,221.0	131,845.0	132,205.0	134,921.0	133,739.0

^aSource for 1981–1982 data is (7); 1983–1985 data (8).

^bValues for this category are in millions of pounds.

pany said in a 1984 interview, “I feel there is a genuine opportunity to expand the numbers and types of people who are using smokeless tobacco” (21). A 1983 article in *Advertising Age* described a new urbane marketing strategy for U.S. Tobacco and quoted the company’s marketing services director as saying, “What we’re doing is directing oral tobacco at an entirely new demographic group” (19). The text of a 1973 advertisement from U.S. Tobacco clearly reveals the company’s attempt to broaden the demographic appeal of its SLT products:

“It’s easy to see why cowboys are into ‘smokeless tobacco.’ And scientists and lab technicians are using it, too. . . . Even lawyers and judges are taking it into their courtrooms. Students and teachers enjoy it in their classrooms” (22).

The Skoal Bandits line was introduced to the New York market with considerable fanfare in the summer of 1983, with expenditures of \$150,000 for a single day’s publicity events and \$2 million or more for related activities in the New York area over that summer (19, 20, 23). Consistent with a strategy to gain customers outside the traditional rural, backwoods market, advertisements began to feature white-collar models and to appear in more general circulation magazines, including *TV Guide* and the *National Enquirer*, as well as in major newspapers. Televised spots during the 1984 Winter Olympics featured male models with a “big city” image (9).

The advertisements suggested that SLT is an acceptable alternative to cigarette smoking. Television and print ads included such slogans as: “Take a pouch instead of a puff” (24). “Just a pinch between your cheek and gum will give you real pleasure—without lighting up” (25). “When you can’t smoke but you want to enjoy tobacco, try Skoal Bandits” (26).

Another common theme was the ease of using SLT (fig. 1). The text of a brochure included with a Skoal Bandits product display read: “It’s as easy as 1-2-3 All you do is put it between your cheek and gum—the refreshing taste comes right through.” Some advertisements provided instructions for use, such as the one in 1980 (20) titled, “Walt Garrison answers your questions about smokeless tobacco.” The text posed such questions as, “Walt, just what is Moist Smokeless Tobacco?”; “How do you use it?”; and “Is it hard to use?” The printed reply to the last question was, “When you first try it, the tobacco may move around

in your mouth more than it should, and your mouth may water a bit more than you’re used to, but getting the hang of ‘going smokeless’ is all part of the fun. In a couple of weeks, you’ll be a ‘pro’” (fig. 2).

Around the time that the Skoal Bandits brand was introduced in 1983, the president of the tobacco division of U.S. Tobacco candidly described the intended “graduation process” for consumers using his company’s various brands of snuff (27). Consumers could begin with Skoal Bandits, in its easy-to-use tea-bag format, then progress to Skoal itself, and finally on to Copenhagen, the strongest of their snuff products.

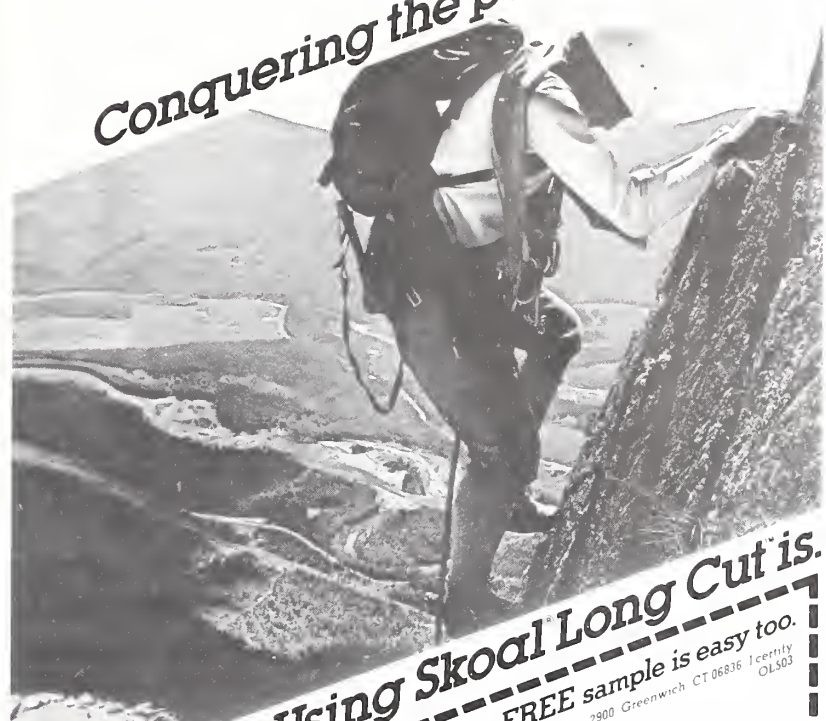
PROMOTIONAL EFFORTS

Coupons for free SLT samples have frequently been incorporated into magazine advertisements (fig. 3), with accompanying slogans that include “Something for nothing” (28), “Try it for free!” (29), or “. . . have a dip on us” (30). A 1985 advertisement read, “Shooting the rapids ain’t easy. Using Skoal Long-cut is. Getting a FREE sample is easy too” (31). Free samples have also been distributed in public places and at events such as rodeos, auto races, and other sporting events.

Various other forms of promotion have been used. Swiss Army knives were offered to consumers and retailers by U.S. Tobacco in exchange for a coupon and slide label from Skoal Bandits mint or Skoal Long-cut mint and \$2 (32). The Skoal Long-cut Sportsman’s Choice Sweepstakes in 1985 included a grand prize of transportation and lodging expenses plus \$500 for a fishing trip for two in Alaska, Canada, or Costa Rica. To enter the competition, one had to submit the answers to three questions (fig. 4) to U.S. Tobacco: “1) What flavor is Skoal Long-cut? 2) Who makes Skoal Long-cut? 3) How many colors are on the Skoal Long-cut can?” (33). In the spring of 1986, U.S. Tobacco sponsored the “Once in a Lifetime Liberty Sweepstakes,” which offered consumers the chance to win one of five all-expense-paid trips for two to the Fourth of July Statue of Liberty rededication ceremonies. Entry blanks for the contest, which was intended to promote Copenhagen SLT, appeared in popular magazines (34, 35).

Apparel and other items bearing product logos are available free or for purchase, as advertised in popular magazines (36, 37). Offers for free merchandise and gift catalogs are commonly included in advertisement coupons (29). A brochure entitled “Smokers Traders” features items bear-

Conquering the peak ain't easy.




Using Skoal Long Cut is.

Getting a **FREE** sample is easy too.

Send to: Skoal Long Cut, P.O. Box 2900, Greenwich, CT 06836. I certify OL503

Some things in life aren't easy to do. But they're sure enjoyable. Skoal Long Cut is both easy and enjoyable. It's not chewing tobacco—Long Cut means that it packs easy, stays put between your cheek and gum. So Skoal Long Cut makes it easy to enjoy tobacco without lighting up. You can get it in wintergreen or mint. Either way, the taste is nice and easygoing, too.



Easy to use. Great taste.

NAME _____ ADDRESS _____ CITY _____ STATE _____ ZIP _____

TELEPHONE NO. _____

Are you a regular user of any moist smokeless tobacco? Yes ☐ No ☐

If yes, what brand? _____

FREE CATALOG MERCHANDISE CATALOG SEND YOUR NAME, ADDRESS & AGE TO: SKOAL LONG CUT, P.O. BOX 2900, GREENWICH, CT 06836. NO PURCHASE NECESSARY. LIMIT ONE PER PERSON. OFFER ENDS 12/31/85.

FIGURE 1.—Advertisement promoting the ease of using SLT.

ing U.S. Tobacco product logos, including hats, automotive aprons, car protectors, and golf bags.

Underwriting sporting events has been a major form of promotion. Professional racing car drivers such as Coca Cola 500 winner Benny Parsons, Indianapolis 500 winner A. J. Foyt, and NASCAR driver Harry Gant (38–40) have been sponsored by companies producing SLT. In 1984, U.S. Tobacco sponsored five of the starting cars at the Indianapolis 500. Exposure of cars bearing the Skoal Bandits and Copenhagen logos on the telecast of the race has been estimated at over \$500,000 in advertising value, not including promotional benefits derived from other broadcasts of the race and the appearances of product logos in related stories in *Sports Illustrated*, *People Weekly*, and elsewhere. Publicity surrounding Italian driver Teo Fabi's pole position in a Skoal Bandits car in the 1983 Indianapolis 500 race was thought to be worth close to \$3 million (41).

In professional baseball, U.S. Tobacco has presented the Skoal Pinch Hitter of the Year award. An announcement of the 1985 award in the *The Sporting News* added, "For a hit pinch, try Skoal" (42). Skoal also sponsored the 1985 season broadcasts of the Atlanta Braves' baseball games on cable station WTBS, which reaches over 26 million homes in the United States (43). Even after he stopped appearing in advertisements for SLT products, former professional football player and rodeo star Walt Garrison continued as spokesman for U.S. Tobacco, and, in 1985, former Miami Dolphin Nick Buoniconti became president and chief operating officer of U.S. Tobacco (10).

Although currently active athletes no longer appear in the ads, the companies continue to link sports with SLT, and they encourage professional athletes to use their products. For example, visors bearing the labels "Skoal Bandits" and "World Champion 49ers" were produced in 1985. A sur-

Walt Garrison answers your questions about smokeless tobacco.

Q: Walt, just what is Moist Smokeless Tobacco?

A: It's just what it says: Tobacco you enjoy without lighting up.

Q: How do you use it?

A: First, you don't chew it. Just take a small pinch between your thumb and forefinger, put it between your cheek and gum, and leave it there. The tobacco will slowly release its great flavor to give you real tobacco satisfaction.

Q: Is it hard to use?

A: Not really. When you first try it, the tobacco may move around in your mouth more than it should, and your mouth may water a bit more than you're used to, but getting the hang of "going smokeless" is all part of the fun. In a couple of weeks you'll be a "pro."

Q: Is there a difference between the three most popular brands?

A: Sure... **HAPPY DAYS** is a mild, satisfying blend of mint-flavored tobacco, while **SKOAL** is full-bodied with the added good taste of wintergreen. **COPENHAGEN** is a stronger, natural blend of choice tobaccos.



All three are packed in convenient cans and each is dated for freshness.

Q: Is the date on the can the expiration date?

A: No, it's the date of manufacture. It's our way of letting you know how fresh and moist our tobacco is.

Q: How much does "Going Smokeless" cost?

A: An average user "dips" about 1½ cans per week, and that's about a dollar's worth. Not bad, when you think how much everything else costs these days.

Q: Do a lot of people use smokeless tobacco?

A: A lot more than you think. Last year we sold over 325 million cans. And more and more people from every part of the country are "going smokeless" all the time. (Even loose-leaf chewers are mixing it in with their brands for extra flavor.)

Q: Where can I buy it?

A: Ask for it at your favorite tobacco counter; or mail the coupon below and you'll get a free can of **HAPPY DAYS** to try.

Thanks a lot, Walt...

A pinch is all it takes!



FIGURE 2.—Advertisement providing instructions on the use of SLT.

vey of major and minor league baseball teams conducted by the Public Citizen Health Research Group in February 1985 found that almost all the teams responding (30 of 32) answered yes to the question, "Do manufacturers of chewing tobacco and tobacco snuff provide these products to your team free of charge?" (Greenberg A: Personal communication). Well-known race-car drivers continue to drive cars emblazoned with SLT logos on national television.

CORPORATE CONTRIBUTIONS

Manufacturers of SLT have cleverly created links between their harmful products and some of our most valued social institutions. With its pledge of \$10 million (44), U.S. Tobacco was the largest corporate contributor to the

Statue of Liberty restoration program, and snuff tins bore the Statue of Liberty "funding sponsor" logo. The company also contributed \$15,000 to a Farm Aid concert, and a blow-up of the company's check was displayed by Willie Nelson (45). In the mid-1980s, over one-half of U.S. Tobacco's charitable contributions went to health and human services agencies, including United Way, Yale Medical Center, Greenwich Hospital, the Alcoholism Council, Save the Children Foundation Inc., the New York Public Library, and Meals on Wheels (46).

Similar efforts on the part of the cigarette manufacturers have been viewed as attempts to gain legitimacy, innocence, and institutional dependence on the industry (47-49). Such public relations efforts would certainly seem to diffuse or

silence criticism of the SLT industry's fundamental enterprise. Indeed, industry executives have been praised for their public service (50).

Ironically, U.S. Tobacco has contributed to drug prevention programs and has actively supported the National Federation of Parents for Drug-free Youth. Moreover, its second-quarter report for 1985 states that the company contributes to drug prevention and alcoholism programs in the belief that "addiction is one of the most serious problems confronting American families today" (46). Thus the company has become identified with anti-drug abuse and alcoholism programs even as it promotes an addictive and harmful substance.

EVIDENCE OF SMOKELESS TOBACCO PROMOTION TO YOUNG PEOPLE

The Smokeless Tobacco Council has adopted its Advertising and Sampling Code. The Council maintains that the

industry has stopped using currently active athletes and employs only models who are 25 years of age or older for its advertisements and commercials. A public service relations promotion from the Smokeless Tobacco Council that appeared in *The Washington Post* in 1985 stated that "chewing tobacco and snuff are intended for adults only." It defined "adult" as age 18 and older.

Official policy notwithstanding, a number of industry activities appear to be youth oriented, e.g., manufacturers of SLT have sponsored tobacco-spitting contests, with teenagers as active participants, and company representatives handed out free samples as well as frisbees and T-shirts in southwest Connecticut (51, 52). By defining an adult as someone 18 years of age or older, the industry has given itself permission to promote its products among older teens and college students. In the name of Copenhagen/Skoal, U.S. Tobacco has contributed \$135,000 annually in college scholarships in conjunction with the Na-

The Mint Choice.

BANDITS SKOAL
Easy-to-use pouch.

SKOAL
LONG CUT
Easy-to-use pinch.

The taste of mint in smokeless tobacco.

Sample them both for free.
For your free sample of both Skoal Long Cut Mint and Skoal Bandits Mint fill out and send to:

THE MINT CHOICE, Dept. #SH 501
Box 2900, Greenwich, CT 06836

Name _____
Address _____
City _____ State _____ Zip _____
Telephone _____

Are you a regular user of any smokeless tobacco? Yes _____ No _____
If yes, what brand? _____ I certify that I am _____ years of age *

*Offer not available to minors. Offer good only in U.S.A. Please allow 4-6 weeks delivery. Offer void where prohibited by law.

© 1985 U.S. Tobacco Co.

Look for the special "Mint Choice" display wherever Skoal Bandits and Skoal Long Cut are sold for a valuable premium offer.

FIGURE 3.—Advertisement incorporating coupons for free samples.



LONG CUT
invites
"SPORTSMAN'S CHOICE"
SWEETSTAKES

Choose
SKOAL
LONG CUT

• Easy to Use • Great Taste

GRAND PRIZE: One week for two at one of the above "Sportsman's Choice" locations. All transportation and lodging expenses are paid. \$500.00 additional cash (incidental expenses).

100 FIRST PRIZES: Choice of **Berkley** Lightning Rod fishing pole and matching **Trilene xt** Line

100 SECOND PRIZES: **Gott** Sportsman Cooler

For a free sample of Skoal Long Cut, write to Skoal Long Cut, Box 2900, Greenwich, CT 06830. Enclose your name, address, age, and the words "Dept. OL 501" on your request. Allow 4-6 weeks for delivery. Offer good only in U.S.A. Offer not available to minors.

OFFICIAL RULES: NO PURCHASE NECESSARY. Here is all you have to do:
1) a 3" x 5" card or piece of paper, hand print your name, address and zip code, and answer the following questions (Answers may be found on can of Skoal Long Cut): 1. What flavor is Skoal Long Cut? 2. Who makes Skoal Long Cut? 3. How many colors are on the Skoal Long Cut can? In the event you do not have a can of Skoal Long Cut, you can send in for a label by writing to UST Marketing Communications, 100 West Putnam Avenue, Greenwich, CT 06830. 4. Enter as often as you wish, but mail each entry separately (only one entry per envelope) to: SKOAL LONG CUT SPORTSMAN'S CHOICE SWEETSTAKES, P.O. Box 9742, Bridgeport, CT 06699. Entries must be received by July 30, 1985.
Winners will be selected in random drawings conducted by an independent judging organization, whose decision is final. Sweepstakes open to persons 18 years and over. Employees and their families of U.S. Tobacco Co., their dealer, distributor, and advertising agencies are ineligible.
VOID WHERE PROHIBITED by law or regulation. All federal and local regulations apply. Winners will be notified by mail, and odds of winning will depend upon the number of entries received. No substitutions or prizes allowed unless offered by the judging organization, whose decision in such matters is final. Taxes on the prize responsibility of the winner. Winners may be required to sign an affidavit of eligibility.
2. In place of prize, institute permits use the name, photograph, and address of winners for purposes of advertising and trade for further compensation. 3. For names of winners, send a stamped self-addressed envelope to: Skoal Long Cut, Sportsman's Choice, Sweepstakes, UST Marketing Communications, 100 West Putnam Avenue, Greenwich, CT 06830.

FIGURE 4.—Advertisement featuring a contest with prizes.

tional Intercollegiate Rodeo Association (53). An article on rodeo scholarships from the June 1985 issue of *Better Homes and Gardens* featured a picture of U.S. Tobacco's three brands of snuff (54). Moreover, U.S. Tobacco had a College Marketing Program, which included having college students serve as campus representatives for free sampling activities as well as sponsoring spring break activities (55). The 1973 U.S. Tobacco advertisement quoted earlier (22) that claimed "Students and teachers enjoy it in their classrooms" is an overt indication of youth targeting. Promotional materials prepared in conjunction with recent attempts to market Skoal Bandits in Scotland included the sentence, "Like your first beer, Skoal Bandits can be a taste that takes time to acquire and get the most out of." Louis Bantle, chairman of the board of U.S. Tobacco Company, once told a reporter, "In Texas today, a kid wouldn't dare

go to school, even if he doesn't use the product, without a can in his Levis" (56). A May 1985 report on the U.S. Tobacco Company issued by Montgomery Securities speculated that "the 18- to 25-year-old age group has been a key element in the company's growth, with Skoal and Copenhagen each benefiting as males in their early prime move to demonstrate their masculinity" (57).

LEGISLATIVE EFFORTS TOWARD REGULATION OF ADVERTISING AND PROMOTION

The SLT products were not affected by the Federal Cigarette Labeling and Advertising Act of 1965 that resulted in a mandatory health hazards warning label on cigarette packages. Nor did the consent orders negotiated by the Federal Trade Commission in 1971-1972 to require warning labels on cigarette advertisements apply to SLT.

The ban on radio and television advertising that went into effect in January 1971 likewise applied only to cigarettes and not to other forms of tobacco.

In June 1984, U.S. Tobacco yielded to the order of the New York State Attorney General barring the company from using the slogan "Take a pouch instead of a puff" in its advertising of Skoal Bandits. The Attorney General held that "The slogan, used without further qualification, implies that the product is a safe alternative to cigarette smoking when it is not." The slogan had appeared in commercials aired during coverage of the 1984 Winter Olympics, in print advertising, in subway posters, and on tote bags distributed at Yankee Stadium (10, 58).

The Public Citizen Health Research Group filed a petition in February 1984 with the Federal Trade Commission asking it to require health warnings on all packaging and advertising for SLT products (17). A year later, in January of 1985, the Federal Trade Commission asked the Surgeon General for a full-scale investigation of scientific evidence on the dangers of snuff and chewing tobacco.

Considerable legislative activity in 1985 at the state and federal levels was designed to require warning labels, prohibit SLT advertising via the broadcast media, prohibit free distribution of products, and ban sponsorship of sporting events by SLT companies (11, 12, 59). The State of Massachusetts ruled in 1985 to require the following warning label on all packages of snuff: "Warning: Use of snuff can be addictive and can cause mouth cancer and other mouth disorders." At the federal level, a bill to ban radio and television advertising of SLT products and to require three rotational warning labels on them and in advertisements passed both houses of Congress and was signed into law (P.L. 99-252) in early 1986. The warning labels read: "Warning: This product may cause oral cancer." "Warning: This product may cause gum disease and tooth loss." "Warning: This product is not a safe alternative to cigarettes."

The American Medical Association, American Public Health Association, American Academy of Pediatrics, and the major voluntary health organizations have all taken the public position that SLT advertising should be banned. A bill introduced into the U.S. House of Representatives in 1986 called for a total ban on the advertising and promotion of all tobacco products (H.R. 4972). Congressional oversight hearings on tobacco advertising and promotion have since been under way.

CONCLUSIONS

Among the many parallels between the history of advertising and promoting cigarettes and that of SLT are:

- Use of sports figures and other celebrities for product promotion,
- College campus marketing programs and other youth-oriented activities,
- Adoption by industry of voluntary codes officially condemning advertising and promotion to children,
- Implication of product safety in advertisements,
- Debates over proposed requirements for health hazards warning labels and bans on radio and television advertising, and
- Sponsorship of socially valued events and institutions.

Unlike cigarette advertising, however, advertisements for SLT have not been directed to women. More information about the target audiences of advertising and promotional efforts is needed, especially if we are to ascertain the effect of such efforts on use patterns by various groups. We need to assess the impact on youth of sponsorship that permits such product logos to be visually associated with sports. Many will watch with great interest the impact of legislation to mandate SLT warning labels and restrict advertising. For example, will implementation of the ban on broadcast advertising of SLT result in dramatic increases in print advertising, as was true for cigarettes in the 1970s, and will there be increases in other forms of promotion? If such changes in industry strategy can be documented, they should be taken into account in any future attempts of investigators to examine the effects of legislation on the prevalence of SLT use.

Many of the recent changes in SLT advertising and promotion (removal of active athletes, withdrawal of the "Take a pouch instead" campaign, and the like) have come about as the result of the airing of public concerns. Continued monitoring of advertisements for themes and validity of claims is necessary for the ongoing formulation of public policy on tobacco advertising.

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Development and Evaluation of a Smokeless Tobacco Cessation Program: A Pilot Study^{1, 2}

Elizabeth Eakin, Herbert Severson, and Russell E. Glasgow^{3, 4}

ABSTRACT—A multicomponent, cognitive-behavioral intervention program, offered to 25 chronic, adolescent male users of smokeless tobacco, was divided into three sessions and involved self-monitoring of smokeless tobacco use, awareness of health risks, behavioral coping strategies, frequent phone contact, and relapse prevention training. Biochemical (carbon monoxide and cotinine) verification of self-reports was obtained, information about subject and environmental characteristics collected, and a 3-month follow-up conducted. Twenty-one of the 25 subjects completed treatment; 9 participants were abstinent at the conclusion of the program, and 4 remained successful in quitting at the 3-month follow-up. Participants who did not achieve complete abstinence reported substantial reductions in smokeless tobacco use, and no increase in cigarette consumption occurred as a result of reducing or quitting use of it. Subjects successful in achieving cessation had consumed a smaller amount of smokeless tobacco at baseline and were more likely to be involved in school athletics.—NCI Monogr 8:95-100, 1989.

Although SLT was once extolled as being a relatively harmless substance, we now have sufficient evidence, both epidemiologic and experimental, to conclude that its use increases the risk of oral cancer and that this risk increases with the degree of exposure (1, 2). In addition to the health hazards directly associated with SLT, its use may increase the probability of subsequent cigarette smoking or use of other nicotine-containing substances (3, 4).⁵ At the time this study began, no reports of experimental evaluations of programs for the prevention or cessation of adolescent SLT use had been published. One recent report of an SLT cessation program for young adults, which was an adaptation of the American Cancer Society's "Fresh Start" adult smoking cessation program, reported a 6-month success rate of only 2.3% (5).

A few investigators (6, 7)⁵ have found consistency between the correlates of SLT use and those of cigarette

smoking among male adolescents. These results suggest that the components involved in smoking cessation programs are applicable to adolescent SLT use. Although considerable research has been devoted to *adult* smoking cessation, few studies have focused on adolescents in respect to smoking cessation programs (8, 9).

The primary purpose of our study was to develop and evaluate a cessation program for adolescent users of SLT. Based on feedback and experience gained from pilot work, a three-session group intervention program was developed. Our secondary goal was to identify variables that might predict treatment outcome. For example, questions such as whether initial number of dips per day at the beginning of the program or years of SLT use were predictive of success in quitting were investigated. Similarly assessed was whether subjects who were not successful in quitting had higher than average levels of alcohol, marijuana, and other drug use.

Concern has been voiced that efforts aimed at SLT cessation should not be undertaken until more is known about the underlying psychosocial factors involved in its use (10). Although dissemination of large-scale cessation programs would be premature, a pilot study such as the one described below can help illuminate the underlying aspects of adolescent SLT use and provide preliminary information about the efficacy of a treatment program for users. For example, sports participation has been hypothesized as being positively related to SLT use (11). In this study, the relationship of sports participation to cessation attempts was also explored.

METHODS

Subjects, recruitment, and therapists.—The majority of the 25 subjects (80%) were recruited from local high schools by referrals from counselors, health teachers, and coaches. Two subjects were referred by local dentists, and 3 were referred by a subject in one of our initial groups. The contact persons (e.g., the teachers, dentists, etc.) were given packets containing information about the cessation program and parent/participant consent forms. They gave these packets to male adolescents who they knew to be "chewers," and kept a list of the names and telephone numbers of potential subjects who were willing to be called by a staff member of the Oregon Research Institute. Inclusion criteria were that the subjects had been daily users of SLT for a minimum of 6 months prior to entering the program and were between 13 and 19 years of age.

Subjects ranged in age from 14 to 18 years and had used SLT regularly for an average of almost 3 years. The mean

ABBREVIATION: SLT = smokeless tobacco.

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³Oregon Research Institute, 1899 Willamette St., Eugene, Oregon 97401. Address reprint requests to Herbert Severson, Ph.D.

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⁵Dent CW, Sussman S, Flay BR: Manuscript submitted for publication.

number of dips per day at baseline for the entire sample was 5.78 (SD = 3.1). Five of the subjects were also daily smokers. Twenty-three subjects (92%) indicated occasional to weekly use of alcohol or marijuana, and 16 (64%) indicated use of other substances in the past 6 months. Fourteen (56%) participated in high school athletics.

Of the three counselors, one female and one male were advanced undergraduate research assistants who had been trained in cessation counseling; the third counselor was a psychologist and research scientist in charge of the study.

Design.—Due to the formative stage of this research, a within-subject, replicated AB design was used (12). Each subject was measured at baseline (A) and then during and after treatment (B). A quasi-experimental comparison group of 11 subjects, for whom treatment was delayed, also provided a crude standard for our evaluating quit rates associated with the intervention. As had been expected, not all 25 subjects were recruited at the same time, and 11 were assessed while they were waiting for treatment. The within-subject design allowed for commencement of a treatment group each time the necessary number of subjects (3–6) for a group was recruited. The inclusion of a randomized control condition would have significantly increased confidence in the results of this study; however, we found it impossible to recruit enough subjects to constitute a sufficiently large control group, given the considerations of statistical power. Although the replicated AB design is methodologically weak, the percentage of successful outcomes will provide some degree of confidence that the treatment is effective, especially given low base rates of cessation of adolescent SLT use (10, 13).

Procedure.—Adolescents who gave their permission to be contacted were telephoned by the first author. They were given an overview of the program, and verbal intent to volunteer for the program was obtained. Twenty-five of 34 persons contacted by telephone agreed to participate. They were then asked to estimate their frequency of SLT use and cigarettes during the past week. It was explained that this information was confidential and that it would be destroyed should they decide not to participate in the cessation program. The students were encouraged to return an informed consent form, which required both subject and parent signatures before baseline data collection began.

Baseline data were collected during the week before the first treatment session; subjects were called three to four times and asked how many dips (and cigarettes) they had had that day and the preceding day(s). They were requested to dip (and smoke) at their normal level and not to attempt to quit during that week. A 15-minute pretreatment interview was also conducted over the phone. During this phone call, subjects were reminded that they were expected to quit on the day of the first treatment session. They were asked if they felt comfortable with that expectation and if they anticipated having any problems in quitting.

A treatment group was formed each time at least four consent forms were received. Two groups were seen initially in March 1986. Subjects whose consent forms were received while these 2 groups were in treatment were told that, because of scheduling constraints, they would be put on a waiting list and that, if they did not quit on their own

volition while waiting to enter the program, they would be seen when the first 2 groups had completed the program. Subjects on the waiting list were called once a week and asked if they were still “chewing,” and, if so, how many dips they had had the previous week.

Treatment.—The intervention consisted of three small group meetings with 2–6 participants, 2–3 counselors, and lasting 1–1½ hours. There was 1 week between the first and second sessions and 2 weeks between the second and third sessions. The 6 students who missed a session during the program were given the opportunity to come to a make-up session.

Session I began with a program orientation in which subjects were told that they would receive a \$10 payment at the end of the program, regardless of the degree of success in quitting. Confidentiality procedures were reviewed, and subjects were encouraged to be honest so that we could do our best to help them quit. The two primary treatment components were discussed: subjects’ motivation to quit and the acquisition of coping skills, which would help make quitting easier. Subjects were asked why they wanted to quit and were reinforced for their participation in the program. A discussion of previous attempts to quit ensued that emphasized learning from past quitting attempts. Then a discussion of previous attempts to quit and current chewing situations followed that focused on having the participants identify situations in which it would be most difficult for them to resist taking a dip. Coping skills for SLT cessation (e.g., “the 4 A’s”: Avoid, Alter, Alternatives, Activities) were introduced. Subjects selected the skill(s) they thought would work best for them and were asked to explain specifically how they would use such strategies to cope with high-risk situations without dipping. It was stressed that if one of the coping strategies did not work, another probably would.

Subjects were asked to rate their motivation to quit and their confidence that they would not be dipping a year from that date on 10-point scales. They then completed a Smokeless Tobacco Use Scale while the counselors collected saliva and breath samples. This was a standard procedure at every session and follow-up. It was explained before the saliva and breath tests that the samples obtained would be analyzed for cotinine and carbon monoxide and would provide a measure of how much subjects had dipped and smoked in the last several days. This “pipeline” procedure has been demonstrated to increase the self-reported use of cigarettes and was presumed to encourage more honest self-reports of chewing (7). The subjects were given a copy of the “Big Dipper” video on SLT (14) and asked to watch it with their parents sometime before session II. The few subjects without a VCR in their homes arranged to watch it with a friend or neighbor who had one. They were told that session II would take place in 1 week and that they would receive three phone calls during the week to check on their progress, problem-solve any difficult situations, and encourage them to continue their quit attempts. Each student completed a standardized 65-question drug survey before leaving.

Much of session II was devoted to a discussion of their progress in quitting: their successes and difficulties. This included a debriefing of slips in which subjects were asked to

describe the stress situation and to suggest a strategy that would enable them to handle that situation without dipping (15). Group problem-solving was encouraged. The view that one slip does not represent the end of their quitting attempt (16) was emphasized. Review of subjects' impressions of the video program was followed by discussion of the health risks of SLT use and parental support of the subjects' attempts to quit. A Quitting Reward Contract was distributed; it was proposed that subjects might want to enlist their parents' support of their quitting by contracting with them. They were told that the third and final session would take place in 2 weeks and they would receive three phone calls during that time. The students then identified any particularly difficult situations they anticipated during the coming weeks, and the group problem-solved these.

The final session began with a discussion of progress in quitting in which slips were debriefed and coping strategies were generated by the group. Subjects who had successfully quit were encouraged to share the strategies that had worked for them. Options were discussed for those who had cut down but had not quit; these included continuing their efforts to quit completely (the preferred option) or maintaining their current low level of dipping. The counselors suggested that these subjects work on quitting completely because of the danger of occasional dipping gradually increasing into regular use of SLT. All subjects completed a "Practice Makes Perfect" exercise (see Dependent and Predictor Variables sections), which was presented as a method of rehearsing the coping strategies that would help them think on their feet and make it through difficult situations. The group then discussed implementation of the quitting contracts distributed in session II. The schedule of follow-up phone calls was explained, and subjects were told that the counselors would be glad to continue working with them on quitting during those phone calls. They were paid \$10 for their participation in data collection activities as they departed.

Follow-up contact.—A series of eight follow-up phone calls were conducted during the 3 months after treatment (one call/wk for the first mo, and one call every other wk during the second and third mo). During these calls, subjects were asked to report the number of times they dipped, smoked cigarettes, drank alcoholic beverages, and the number of times marijuana was smoked during the previous week(s). For subjects who expressed the need for help in problem-solving and encouragement regarding their continued efforts to quit, these phone calls also included counseling on handling difficult situations and refraining from SLT use. The average length of a phone call was approximately 5 minutes.

Subjects were paid \$5 to participate in each of the 3-month follow-up meetings, and \$10 to attend the 6-month posttreatment meeting. During those meetings, discussion centered on subjects' progress in abstaining and collection of saliva and breath samples.

Dependent variables.—Primary dependent variables were the number of 1) self-reported dips and cigarettes smoked, 2) alcoholic beverages consumed, and 3) times marijuana was used. Subjects were asked to monitor these activities, but they were not asked to keep a continuous written record

of these behaviors.⁶ Cotinine content in saliva verified reports of SLT use. The saliva samples also served to encourage subjects' honesty in self-reporting (17). We analyzed breath samples for carbon monoxide on a Mini CO gas analyzer to corroborate self-reported cigarette and/or marijuana smoking.

Predictor variables.—Information about various subject and environmental characteristics was collected including: motivation and degree of confidence at session I, the Smokeless Tobacco Use Scale, drug use survey, and the number of close friends who chew. Addiction was assessed with an eight-item adaptation of the Fagerstrom Tolerance Questionnaire (18), which has been widely used in smoking cessation research.

RESULTS

Outcome

Of the 25 subjects who began treatment, 21 completed the program. Nine of the 21 (43%) who completed treatment or 36% of those who started in the program were successful in quitting by the final session. Success was defined as a self-report of one slip or fewer during the week before the end of treatment and a verifying cotinine analysis (8 reported no slips, and 1 reported one slip).

Saliva samples collected at the final treatment session were analyzed for cotinine, which is a primary metabolite of nicotine. Cotinine in saliva has a half-life of approximately 20 hours (Benowitz NL: Personal communication). A nonuser of tobacco would not be expected to have a saliva cotinine level over 10 ng/mL. A saliva cotinine level of 10 ng/mL is considered a "grey zone," and levels greater than 25 ng/mL indicate use of tobacco products within the past 20 hours.

Because of the disparity between the definition of end-of-treatment success (e.g., one slip or fewer during the wk prior to the end of treatment) and the 20-hour half-life of cotinine, the results of the saliva samples cannot be used as an exact verification of the end-of-treatment success rate. Nevertheless, the data indicate that at least 7 of the 10 subjects who reported having one or no slips during the week before the end of treatment were indeed honest in their self-reports. Of the three remaining subjects, one (No. 4) was in the "grey zone" with 16.7 ng/mL of saliva cotinine; subject No. 7 appears to have been lying (given his value of 86.2 ng/mL); and subject No. 18, with 212.4 ng/mL, smoked a half-pack of cigarettes/day, which makes verification of his self-reported nonuse of SLT impossible. The correlation between self-reported dips during the week prior to the end of treatment and the saliva cotinine analyses was .49. Excluding cigarette smokers from the samples increased this to $r = .87$.

⁶Due to the almost total noncompliance of subjects in an initial pilot study in completing and returning self-monitoring forms, the staff decided not to require "on the spot" self-monitoring. They hoped that the frequency of phone calls would circumvent the problem of inaccurate self-reporting resulting from the students forgetting how many dips they had during a given time.

Figure 1 displays the quitters' and nonquitters' average number of dips/day at baseline and over the course of treatment. At the end of treatment, even the nonquitters had reduced their use of SLT by 77% from baseline levels. There was little evidence of increased smoking associated with reductions in SLT use among smokers at baseline. From baseline, the smokers showed an average decrease of cigarette use of 43% during treatment. However, 1 nonsmoker at baseline began smoking occasionally after the end of treatment. One of the 11 students on the 3-week waiting list quit on his own, and another reduced his average number of dips/day from 7 to 1.8. The remainder (82%) reported no change in dipping behavior while on the waiting list. The subject who quit while waiting for treatment had a number of friends who were participating in the initial cessation program at the same time that he quit on his own.

Six-month Follow-up Outcome

We were able to obtain follow-up information on 20 subjects at the 6-month follow-up. Success in quitting was again defined as one or fewer slips during the week before follow-up and was biochemically verified. Five subjects self-reported abstinence at 6 months. Two of these were confirmed with low saliva cotinine levels, 1 was a daily cigarette smoker, and 2 were not confirmed by cotinine analysis. Thus, conservatively, basing abstinence estimates on all subjects who began treatment and required biochemical verification, we determined a long-term cessation rate of 12%. Those subjects who did not achieve abstinence reduced their daily use of SLT by 45% from baseline levels.

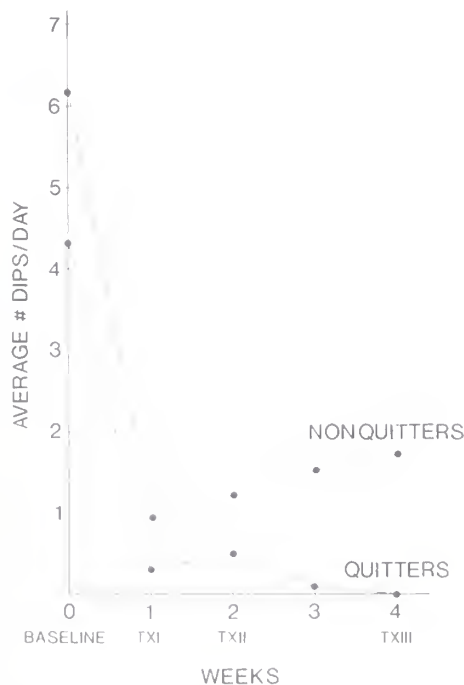


FIGURE 1. Average number of dips per day at baseline and over the course of treatment for quitters and nonquitters.

Predictors of Cessation

Table 1 shows a comparison of those who quit after testing and nonquitters (including the 4 dropouts) on various baseline measures. The quitters had a significantly lower average number of dips/day at baseline than those who did not quit (4.4 vs. 6.4 dips/day, $P < .05$). Eight of the 9 quitters (88%) were high school athletes, compared with 38% of the nonquitters ($P = .022$, Fisher's exact test). Of the 5 subjects who were daily smokers, only 1 was successful in quitting his use of SLT, compared with 8 of 16 nonsmokers. Other measures were nonsignificant given the small sample size, although some means were in the predicted direction.

DISCUSSION

This was a small-scale efficacy study that assessed the feasibility of a multicomponent treatment program adapted from recent developments in the smoking cessation literature in aiding male adolescents to quit using SLT. Although the end-of-treatment success rate of 36% (43% counting only subjects who completed treatment) and 6-month abstinence rate of 24% (29% counting only subjects who completed treatment) were not as high as expected, these results are far from discouraging. When the study began, we had no precedent to follow in designing the program. There is a paucity of literature on smoking cessation with adolescents, and, to our knowledge, no SLT cessation studies with adolescents have been published.

A relatively high-risk group of adolescents participated in the program. Twenty-three of the 25 (92%) reported being occasional to daily users of alcohol, marijuana, or cigarettes, and 16 (64%) indicated use of other hard drugs, such as amphetamines, hallucinogens, or psychedelic mushrooms during the 6 months prior to treatment. In addition, 1 subject moved out of his parents' home because of family conflict, another was expelled from school and began attending a "continuation school," and 2 attended night school in addition to their regular classes because of attendance, academic, or behavioral problems. Seven of the 9 adolescents who quit by the end of treatment engaged in a number of problem behaviors (19). As described by Jessor and Jessor, these behaviors include drug use, sexual intercourse, activism, drinking, problem drinking, and general deviant behavior. This fact increases our confidence in the efficacy of our program, because these adolescents are often difficult to keep in treatment and resistant to attempts to change their problem behaviors.

We hypothesized that subjects who were not successful in quitting would be heavier users of SLT, cigarettes, alcohol, marijuana, and other drugs and they would score higher on the SLT addiction scale compared with those who were able to quit. A number of these hypotheses were confirmed: The successful quitters had a significantly lower baseline rate of SLT use than did the nonsuccessful subjects. The nonquitters also had a higher, although statistically nonsignificant, use of marijuana and other drugs than did the students who successfully quit. Given the small sample size, it is not surprising that many of these differences did not reach conventional levels of significance. However, the direction of the data is consistent with what one would expect to find in most substance abuse cessation programs, i.e., that higher levels of use lead to greater difficulty in quitting.

TABLE 1.—Characteristics of 9 quitters and 16 nonquitters^a

Baseline data	Quitters			Nonquitters			Significance tests ^b
	Mean	Percent	SD	Mean	Percent	SD	
Average No. of dips/day	4.4		1.51	6.4		3.4	$t(23) = 1.6$
Athlete		88			38		$P < .10$
Daily smoker		11			25		$P = .01$
SLT use (addiction scale 0–16)	9.3		1.32	12.23		2.97	
Alcohol (No. of drinks/wk)	6.6		7.9	6.4		8.2	
Marijuana (No. of times used/wk)	2.7		1.39	3.6		6.88	
Other drugs (No. of times used 6 mo before treatment)	4.4			5.0			
Quit before		44			68		
No. of five close friends who chew	3.3		1.36	2.8		1.25	

^a The 4 subjects who dropped out of treatment were categorized as nonquitters.

^b We used *t*-tests to contrast groups on continuous variables and Fisher's exact test for categorical variables. Significance was noted only for average number of dips/day and participation in athletics.

Most successful participants seemed ready to quit, as exemplified by the fact that they quit completely (except for an occasional slip) immediately after the first session. Eight of these 9 were members of athletic teams at their schools. In fact, one of the strongest predictors of success was participation in school sports. Perhaps the self-discipline characteristic of athletes was an important factor in their success in quitting. School contingencies related to team membership may also have been a factor in subjects' success in quitting, or at least they were an initial motivator. Twelve of the 25 participants came from the same high school. We first believed that the school's health teacher was responsible for their recruitment. However, he reported that he had done little in the way of recruiting. In fact, students had come to him for information about the program, often at the insistence and prodding of other students. This "pyramid referral" may have been spurred by a number of new substance use rules that were put into effect at the beginning of the school year; these included a mandatory suspension for anyone caught using a substance (including SLT) on school grounds, and an automatic 3-week suspension from the team for any athlete caught using a substance. The recruitment was, by chance, timely, with the school's "crack-down" on student drug use. However, this factor may limit the generalizability of the results, because we could not determine what effect the school's antidrug policy had on our subjects' success in quitting. Future research is needed for an investigation of possible interactive effects between cessation programs and school antidrug policies. This study was also limited by its small sample size and our inability to rule out placebo effects. Additional research with larger samples that would also allow for evaluations of peer group and counselor effects is indicated.

The Big Dipper video and the Quitting Reward Contract were not as successful in motivating the subjects to quit as had been expected. Subjects complained that the video was not graphic enough in its depiction of the health risks

of SLT use, and many did not watch it with their parents. During the course of treatment, only 3 students contracted with their parents, and 2 contracted during the period of follow-up. Most students either forgot about the contract or did not want to do so with their parents. The video and contract might have been more successful had there been more parental involvement in the treatment, such as having the parents attend a special session in which they would learn how to support their sons' efforts to quit.

The present cessation program could be modified in future studies in a number of ways. Many of the changes will likely arise from time constraints. The program as it stands was time-consuming due to the large number of phone calls to the subjects. Although the number of calls (20/subject) could certainly be decreased, these calls and the program sessions may have been the most powerful components of the treatment. Nicotine gum is an option that could be explored for more addicted students experiencing nicotine withdrawal symptoms or other difficulties in quitting. Finally, other avenues of recruitment might be explored. School recruitment was the primary source of our referrals, but some came from local dentists. This professional group can be a valuable source of referrals, because an oral examination can provide a unique opportunity for a dentist to encourage an SLT user to quit the habit (20).

This study suggests that a significant number of adolescent SLT users are responsive to the opportunity to participate in a cessation program. Given the rising number of adolescent users, the authors recommend that any comprehensive drug-use reduction program also address the issue of SLT cessation. We hope this study will provide the impetus for increasing our efforts toward identifying a cost-effective cessation program to help young users to quit.

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Adolescent Smokeless Tobacco Use: Future Research Needs¹

Laurie Chassin,² Clark C. Presson,² Steven J. Sherman,³ and Lynne Steinberg³

ABSTRACT—Future research needs in the area of adolescent smokeless tobacco use are addressed, based on the studies reported in this volume covering methodologic issues and substantive directions. In addition, we outline some implications for developing preventive interventions to deter smokeless tobacco use among adolescents.—NCI Monogr 8:101-105, 1989.

The papers in this volume provide a descriptive data base that is a useful start toward our understanding of adolescent SLT use. The prevalence data obtained from diverse geographic areas and subpopulations clearly document the magnitude of its use among adolescent boys and the recent increases in such behavior patterns. In addition, these papers have identified important correlates of SLT use that will facilitate the development of theoretical models of this behavior. Identifying these correlates helps us to specify the target audience for preventive intervention as well as to suggest potentially modifiable risk factors that will be the focus of these interventions, e.g., attitudes, beliefs, and social influences (1-3).

Although these papers represent a promising beginning, many problems and research questions concerning SLT use remain. We will identify some of these important directions for future work. However, before substantive questions can be raised, several issues pertaining to research methodology must be addressed, but once they have been discussed, directions for future research and implications for intervention can be provided.

METHODOLOGIC CONSIDERATIONS

As the authors of the various papers in this volume note, the present data bases consist largely of cross-sectional correlational surveys of tobacco use behaviors. Although providing good descriptive data, this methodology cannot distinguish the antecedents of a behavior from its consequences, nor can it spell out the mediating factors involved in initial SLT use or continuation. From the standpoint of preventive intervention, it is, of course, the antecedents of the behavior that are most important. The difficulties in interpreting cross-sectional data are illustrated in our studies, in which cross-sectional and longitudinal analyses of the

same sample yielded different patterns of age effects for adolescent cigarette smoking (4).

Cross-sectional and longitudinal analyses can produce different findings for several reasons. For example, cross-sectional analyses can mask potentially important differences between adolescents who are long-standing users and those who have only recently started using tobacco. Thus the factors that lead to the onset of tobacco use are confounded by other factors that act to maintain regular use.

This problem of interpretation is not a new one. It is found in epidemiologic and public health research on disease *prevalence* (all individuals who have a disease at a given period) and disease *incidence* (all new cases of a disease). Prevalence and incidence questions often produce conflicting data. A more detailed discussion of these issues as applied to adolescent cigarette smoking has been presented (4). For our purposes here, the conflicting findings of cross-sectional and longitudinal investigations highlight the need for prospective longitudinal (or sequential) studies that can examine more directly the processes involved in the onset of SLT use. Researchers in this area should use these designs to test specific models of behavior with regard to SLT use.

Within longitudinal studies, its use should be conceptualized as consisting of unique stages of initiation, regular use, and cessation. These stages have been shown to be useful in the study of cigarette smoking (5) in which distinct determinants are associated with each stage. The current common practice of making simple distinctions between "nonuse" and "any use" is problematic. The inclusion of one-time, occasional, and regular uses in a single category will limit the extent to which factors leading to regular use can be identified because the group of users is too heterogeneous. Even within the experimental user category, important differences may be found between a single use and repeated experimentation. Empirically, the significance of a single instance of SLT use has to be established. That significance may be determined by the particular context of that use. For example, a female who participated in a single use of snuff or chewing tobacco for a sorority initiation would be classified as a user. However, in this social context, a single use is unlikely to signal the beginning of more habitual consumption.

Unfortunately, these distinctions between stages and contexts of use can only be made with a large sample size. Given the relatively low base rate of SLT use (especially among females), researchers in the past have not always been able to investigate separate stages and types of use.

Historically, research in SLT use has grown out of studies of cigarette smoking. This history has its advantages because some similarity is likely in the factors and processes involved in both forms of tobacco use. However, it is also

ABBREVIATION: SLT = smokeless tobacco.

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²Department of Psychology, Arizona State University, Tempe, Arizona 85287. Address reprint requests to Laurie Chassin, Ph.D.

³Psychology Department, Indiana University, Bloomington, Indiana 47405.

important that one remember that unique determinants of SLT use cannot be captured by simply measuring general smoking-related variables. It may be these uniquenesses are most important in the design of preventive interventions.

In an investigation of the unique features of SLT use, methodologic questions arise from the natural co-occurrence of its use and cigarette smoking. As mentioned by several authors, the two forms of tobacco use are correlated, although substantial numbers of SLT users do not smoke cigarettes. For example, Ary (6) found that 20% of users were also regular cigarette smokers, substantially higher than the base rate of regular cigarette use. However, most (80%) users of snuff and chewing tobacco did not smoke cigarettes. Thus SLT use is a behavior that has significant overlap with cigarette smoking, but it also has substantial independence from smoking as well.

This overlap with smoking can create methodologic and interpretative dilemmas when researchers set out to study the unique features of SLT use. Simple comparisons between users and nonusers might prove misleading if researchers fail to distinguish between users who do and those who do not smoke cigarettes. Observed differences between user and nonuser groups could be due to the presence of different levels of concurrent cigarette smoking rather than to SLT use itself. For example, our data suggest that adolescent males who use SLT and cigarettes differ significantly from their abstaining peers in their perceived family environments. However, adolescent males who use SLT only do not differ from their abstaining peers on these same variables (7). Thus adolescents who use it in addition to cigarettes (or multiple other substances) may differ in many important ways from those whose use is restricted to snuff and chewing tobacco. Researchers interested in the unique features of SLT use should consider the confounding effects of other substance use when interpreting their data.

Trying to recognize both the commonality and the uniqueness among tobacco use behaviors and between tobacco and other substance use, we will now raise some substantive directions for future research on adolescent SLT use. In each case, we will try to spell out how these directions may also have implications for preventive interventions.

SUBSTANTIVE AREAS FOR FUTURE RESEARCH

Relationship of Smokeless Tobacco Use to Cigarette Smoking

One of the most basic and frequently raised issues concerning SLT use is the relationship of this behavior to cigarette smoking. Previous research (including the studies reported in this volume) indicates that cross-sectional associations occur between the two forms of tobacco use. However, investigators' attempts to unravel the temporal sequence underlying this association have produced findings that are far from clear. One pattern reported by Ary et al. [cited in (8)] is that cessation of SLT use was associated with later smoking. Yet another pattern is suggested by Dent et al. (9) and by Peterson and associates (10). Their data suggest that two pathways occur. Use of SLT increased the probability of smoking onset, just as cigarette smoking increased the probability of initial SLT use.

Despite several efforts, it is clear that we do not have a precise specification of the relationship between cigarette smoking and chewing tobacco and snuff use. Yet understanding of the precise relationship and the temporal sequence involved has important implications. It may be that adolescent males abandon cigarette smoking to adopt SLT use as a perceived safe alternative. If this is the temporal sequence, it may be that our antismoking campaigns have been too narrowly targeted. These antismoking messages could inadvertently increase SLT use by successfully educating the public only about the health dangers of smoking. By focusing only on smoking, we may also have created the impression that SLT use is a reasonably safe option.

An alternative sequence is that its use is a precursor to cigarette smoking. The likely mechanism here would be that SLT would establish a dependency on nicotine and thereby increase the probability of cigarette smoking. This sequence would imply that prevention programs ought to be aimed more directly at SLT use and perhaps that consciousness should be raised about the nicotine-addicting potential of snuff and chewing tobacco products.

A third possibility is that cigarette smoking and SLT use are functionally equivalent and are associated because of a common third variable pathway, such as motivation for rebelliousness. This possibility is indicated by the results of Dent et al. (9). Such a model would have important implications for public health policy with regard to tobacco use. If these behaviors serve a common purpose, then the use of either can substitute for the other. Unless the underlying common purpose was addressed, interventions aimed only at one of the behaviors would likely lead to an increase in the use of the other. One example of this is interventions that seek to limit the availability and supply of the substance. If marijuana and cocaine use are motivated by identical third variables and if they serve the same functions, then programs aimed at decreasing the supply of marijuana may have the unintended consequence of increasing cocaine use.

These considerations underline the importance of investigators understanding the functions of adolescent SLT use, so that effective prevention programs can be devised. If intervention programs ignore the functions of the target behavior, then these factors will continue to operate and will push people to engage in the behavior. Unless the intervention itself is powerful, it may not override these motivations. For example, fear appeals have been widely but unsuccessfully used to deter cigarette smoking (11). Although these fear appeals may provide temporary motivation, they fail to address the functions that cigarette smoking serves for adolescents. These fear appeals were not powerful enough to override the positive functions of cigarette smoking. Elsewhere, we have discussed in more detail the importance of a functional analysis of substance use for the development of interventions (12). We will now discuss some possible functions of SLT use behavior, many of which have been suggested by other authors in this volume.

Self-image and Social Image Functions

One possible function of SLT use is that it serves to express or achieve certain kinds of images. Our work with

cigarette smoking and SLT use has pointed to the importance of social image factors (13, 14). Use of snuff and chewing tobacco is associated with an image of masculinity, athleticism, bravery, toughness, and love of the outdoors. These characteristics are desirable to considerable numbers of adolescent boys, who may adopt SLT use as a way of projecting this image either in their eyes or in those of their friends. As reported in this volume, it is the image functions of its use that are projected in marketing appeals (15, 16).

One issue raised by some authors is whether SLT advertisements are targeted to adolescent audiences or are aimed only at adults (as claimed by the tobacco industry). Even if they are successful in portraying SLT use as an adult behavior, this does not mean that they will be ineffective in influencing adolescents to use tobacco. One important appeal of tobacco use behaviors may be to project an image of precocity. Thus it may be attractive for these adolescents to engage in a behavior that is defined as strictly adult in nature.

Our work indicates that the use of SLT may help adolescents attain an image that has specific social benefits. If so, preventive interventions cannot be done simply by our teaching adolescents to "say no," because they may lack the motivation to do so. Instead, interventions should provide adolescents with other ways to attain these social image benefits. Leaders of several promising programs in smoking prevention have incorporated social skills training to achieve these goals (17).

Sex-role Image Functions

One part of the social image associated with SLT use involves ruggedness or masculinity. In fact, its use in most subcultures is largely limited to males. One function that it may serve for males is to allow them to engage in a behavior that is explicitly defined as unfeminine. Such a behavior would set them apart from girls and prove or express their masculinity. At one time, a similar function may have been served by cigarette smoking, but with rising rates of smoking among women, sex-typed distinctiveness for cigarette smoking has all but disappeared. To achieve an image of masculinity, adolescent boys may be turning to a different kind of behavior that thus far has not been adopted by adolescent girls.

The sex-typed nature of SLT use raises the question of the meaning or significance of it for females. Studies of cigarette smoking have generally found few sex differences in the dynamics of initiation [although girls have been reported to be more susceptible to social influences (18)]. Burke et al. (2) reported some sex differences in the correlates of SLT use that they found difficult to interpret. They also found that its use by males was more readily predictable from social-psychologic factors than was its use by females. This difficulty in the understanding of female use may result partly from their low base rate. The small number of females who use SLT may be motivated by various idiosyncratic factors rather than a homogeneous set of causes that would be more readily detectable. At this time, female use may be more easily studied in the few subcultures in which it is more common (19). However, we

should not ignore the possibility that the use of SLT may follow the history of cigarette smoking and eventually become widespread among females.

The sex-typed nature of its use may also have implications for interventions. If boys use it partly to project a masculine image, then their image in the eyes of adolescent girls should be extremely important in influencing their behavior. For example, Gritz (20) suggests that information about females' negative reactions to snuff and chewing tobacco could be incorporated into prevention programs.

Parental Influence

Parental influences, of course, have been demonstrated in many areas of substance use, and SLT is no exception. One interesting finding is reported by Bauman and co-workers (1), who observed that at higher levels of father's education more similarity occurred between father and son in its use. In the past, many reported similarity between parents and adolescents in substance use behaviors. However, surprisingly little work has been done on the question of whether such similarity changes with indices of socioeconomic status, such as parental education. The effect of socioeconomic status found by Bauman et al. (1) raises several intriguing possibilities about the processes of parental influence.

First, it is possible that parents in the lower socioeconomic levels are generally less powerful models for their children. In other words, it is possible that similarity (across a range of behaviors) between parents and children is generally less at the lower levels of socioeconomic status. This is consistent with a previous report that adolescents who are poor feel more independent from their parents in various behavioral domains than do those in the middle- and upper-income classes (21). If parental behaviors are, in fact, less imitated at lower levels of socioeconomic status, then further questions arise about the ways in which such status weakens parental modeling effects. One possibility is that status differences in modeling are due to differences in parenting styles across socioeconomic status.

Alternatively, the greater impact of SLT use by a father who has a high level of education might be due to the relative distinctiveness of its use at that level of socioeconomic status. At high levels, generally fewer models for SLT use are observed among adults and peers, so that the presence of a parental model is salient and powerful. However, at lower levels, the adolescent will be exposed to multiple models, and the power of a single parental model might be diminished. If this interpretation is correct, then the reverse finding would be expected when the behavior in question was relatively rare at low levels of socioeconomic status. For example, playing golf may be relatively uncommon for a person who is at the lower levels of socioeconomic status; but in this case, there should be more similarity in playing golf among parents and adolescents in the lower socioeconomic levels than among their higher income counterparts. This interpretation suggests a more general principle that distinctive or unique parental behaviors are imitated more regardless of socioeconomic status.

The finding of greater similarity in parent-child behavior at higher levels of parental education thus indicates several interesting possibilities. First, it may be that parents

of lower socioeconomic status are generally less powerful models. Second, it may be that distinctive or unique parental behaviors are imitated more than common behaviors regardless of status. Although the finding was reported in the context of SLT use, it may have wider implications for the understanding of parental influences on adolescent socialization generally. One side benefit of adolescent SLT use is that its study may evoke more general questions of adolescent development.

Smokeless Tobacco Use as a Problem Behavior

One influential theory of substance use by adolescents has been proposed and tested by Jessor and Jessor (22). According to their problem behavior theory, substance use behaviors represent premature transitions to adult behaviors in violation of age norms. These behaviors are adopted by adolescents who are relatively unconventional, rebellious, and tolerant of deviant behaviors. Support for this position has been obtained from studies of alcohol and marijuana use and cigarette smoking. When a behavior is adopted for these reasons, implications for prevention and intervention are important. For example, this theory suggests that the at-risk group for substance use is relatively deviance prone and unconventional. Such a high-risk group is unlikely to be reached or influenced by traditional school-based prevention programs.

The major question for our concerns is whether adolescent SLT use also represents a problem behavior in Jessor and Jessor's sense of the term. Some evidence indicates that it does not. Our data (14) suggest that SLT use is a behavior that is 1) relatively acceptable to adults compared with other substance use and 2) engaged in openly rather than hidden from parents. In some social contexts, the behavior is even displayed publicly by adolescents and is encouraged by adults, e.g., in tobacco-spitting contests at county fairs. We believe it is impossible to conceive of similar publicly rewarded displays of marijuana smoking or alcohol consumption for young adolescents.

In addition to its relative social acceptability, some data on personality correlates cast doubt on the role of SLT use as a problem behavior. For example, Edmonds et al. (23) found that college students who used SLT were more reserved, more conforming, and less outgoing than nonusers. These are not the personality characteristics of deviance-prone adolescents who engage in problem behaviors.

Another personality correlate relevant to the problem behavior theory is risk-taking, which has been associated with a variety of adolescent drug-use behaviors (24). The evidence with respect to risk-taking and adolescent SLT use is mixed. For example, Sussman and associates (3) found that risk-taking was not a significant prospective predictor of experimentation with its use. However, Dent et al. (9) determined that risk-taking was a predictor of initial use. Thus data on personality correlates are not strongly supportive of its use, per se, as an adolescent problem behavior.

If use of SLT does not represent a classic problem behavior, then such use may be a function of positive socialization rather than of "reactance" and rebelliousness. In this model,

changing the perceived social acceptability of the behavior should decrease its use. If parents 1) were to be better informed about the health risks of the behavior, 2) decreased their use, and 3) were clearly unfavorable to SLT use by their children, then fewer adolescents would use it.

However, it is possible that SLT use represents a problem behavior in some populations and not in others. For example, among rural and agricultural subcultures, such as those represented in the Edmonds et al. study (23), SLT use may represent more of an accepted, normative behavior for adolescent boys than in other subcultures. Even within a single population, it may be that its use represents a problem behavior function for some users and not for others. For example, its use among athletes may not reflect a rebellious, problem behavior.

An understanding of the extent to which SLT use represents a problem behavior in particular subpopulations can have important implications for interventions. For example, Eakin and co-workers (25) determined that an intervention program aimed at users was more successful at a 3-month follow-up for less deviance-prone individuals (i.e., for those who were involved in school athletics and who were less likely to use marijuana). The authors noted that their program impact may have been strengthened by changes in school rules to enact more stringent penalties for SLT use. Such a combination of formal intervention with more broad changes in the school environment (initiated by school administrators) is indeed ideal from the point of view of magnifying and maintaining treatment effects. However, reinforcement from a school setting may be less able to influence deviance-prone adolescents.

CONCLUSIONS

We have pointed to several important directions for future research in the area of SLT use. Methodologically, we underlined the importance of longitudinal studies that look upon its use as a unique behavior (examining the impact of concurrent multiple substance use) and as a process that occurs over time in distinct stages. Substantively, we suggested that researchers examine the temporal sequences underlying the relationship between cigarette smoking and SLT use and the functions of its use (including self-image, sex-role, and problem-behavior functions); they should also investigate different mechanisms of parental influence. To get a better understanding of adolescent SLT use, we focused on developing better theoretical models of these processes as well as refining and testing these process models.

Most work in the area of adolescent substance use arises as a response to an already emergent problem. Thus research and intervention have tended to be reactive rather than proactive. Perhaps researchers should turn to the history of patterns of substance use and to use that information to attempt to anticipate future trends in SLT use behavior.

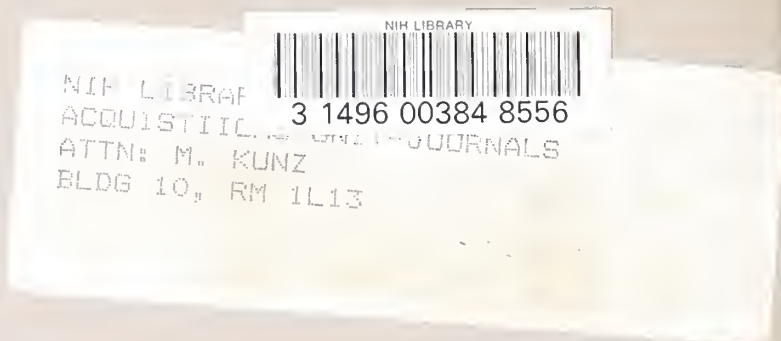
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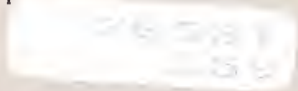
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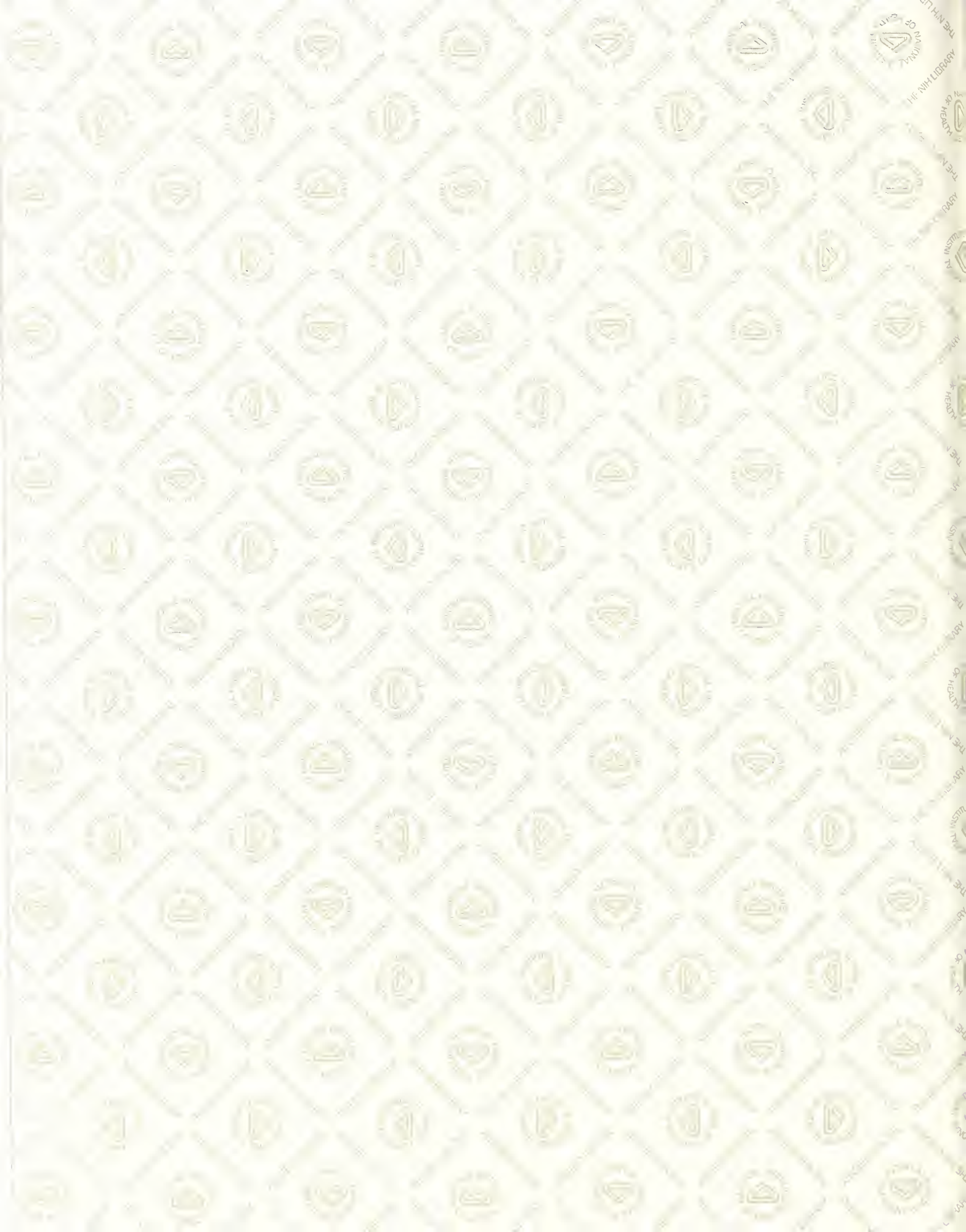


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